

**COMPOUNDS WHICH INHIBIT LEUKOCYTE ADHESION
MEDIATED BY VLA-4**

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 60/108,164, which was converted pursuant to 37 C.F.R. § 1.53(c)(2)(i) from U.S. Patent Application No. 08/904,415, filed July 31, 1997, which application is incorporated herein by reference in its entirety.

Field of the Invention

This invention relates to compounds which inhibit leukocyte adhesion and, in particular, leukocyte adhesion mediated by VLA-4.

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References

The following publications, patents and patent applications are cited in this application as superscript numbers:

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| 10 | ¹ | Hemler and Takada, <i>European Patent Application Publication</i> No. 330,506, published August 30, 1989 |
| | ² | Elices, et al., <i>Cell</i> , <u>60</u> :577-584 (1990) |
| 15 | ³ | Springer, <i>Nature</i> , <u>346</u> :425-434 (1990) |
| | ⁴ | Osborn, <i>Cell</i> , <u>62</u> :3-6 (1990) |
| 20 | ⁵ | Vedder, et al., <i>Surgery</i> , <u>106</u> :509 (1989) |

- 6 Pretolani, et al., *J. Exp. Med.*, 180:795 (1994)
- 7 Abraham, et al., *J. Clin. Invest.*, 93:776 (1994)
- 5 8 Mulligan, et al., *J. Immunology*, 150:2407 (1993)
- 9 Cybulsky, et al., *Science*, 251:788 (1991)
- 10 10 Li, et al., *Arterioscler. Thromb.*, 13:197 (1993)
- 11 Sasseville, et al., *Am. J. Path.*, 144:27 (1994)
- 12 Yang, et al., *Proc. Nat. Acad. Science (USA)*, 90:10494 (1993)
- 15 13 Burkly, et al., *Diabetes*, 43:529 (1994)
- 14 Baron, et al., *J. Clin. Invest.*, 93:1700 (1994)
- 20 15 Hamann, et al., *J. Immunology*, 152:3238 (1994)
- 16 Yednock, et al., *Nature*, 356:63 (1992)
- 17 Baron, et al., *J. Exp. Med.*, 177:57 (1993)
- 25 18 van Dinther-Janssen, et al., *J. Immunology*, 147:4207 (1991)
- 19 van Dinther-Janssen, et al., *Annals. Rheumatic Dis.*, 52:672 (1993)
- 30 20 Elices, et al., *J. Clin. Invest.*, 93:405 (1994)
- 21 Postigo, et al., *J. Clin. Invest.*, 89:1445 (1991)
- 35 22 Paul, et al., *Transpl. Proceed.*, 25:813 (1993)
- 23 Okarhara, et al., *Can. Res.*, 54:3233 (1994)
- 24 Paavonen, et al., *Int. J. Can.*, 58:298 (1994)
- 40 25 Schadendorf, et al., *J. Path.*, 170:429 (1993)
- 26 Bao, et al., *Diff.*, 52:239 (1993)
- 45 27 Lauri, et al., *British J. Cancer*, 68:862 (1993)

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28 Kawaguchi, et al., *Japanese J. Cancer Res.*, 83:1304 (1992)

29 Kogan, et al., *U.S. Patent No. 5,510,332*, issued April 23,
1996

30 International Patent Appl. Publication No. WO 96/01644

All of the above publications, patents and patent applications are
herein incorporated by reference in their entirety to the same extent as if
each individual publication, patent or patent application was specifically and
individually indicated to be incorporated by reference in its entirety.

State of the Art

VLA-4 (also referred to as $\alpha_4\beta_1$ integrin and CD49d/CD29), first
identified by Henner and Takada¹ is a member of the β_1 integrin family of
cell surface receptors, each of which comprises two subunits, an α chain and
a β chain. VLA-4 contains an α_4 chain and a β_1 chain. There are at least
nine β_1 integrins, all sharing the same β_1 chain and each having a distinct α
chain. These nine receptors all bind a different complement of the various
cell matrix molecules, such as fibronectin, laminin, and collagen. VLA-4,
for example, binds to fibronectin. VLA-4 also binds non-matrix molecules
that are expressed by endothelial and other cells. These non-matrix
molecules include VCAM-1, which is expressed on cytokine-activated
human umbilical vein endothelial cells in culture. Distinct epitopes of VLA-
4 are responsible for the fibronectin and VCAM-1 binding activities and each
activity has been shown to be inhibited independently.²

Intercellular adhesion mediated by VLA-4 and other cell surface
receptors is associated with a number of inflammatory responses. At the site
of an injury or other inflammatory stimulus, activated vascular endothelial
cells express molecules that are adhesive for leukocytes. The mechanics of
leukocyte adhesion to endothelial cells involves, in part, the recognition and
binding of cell surface receptors on leukocytes to the corresponding cell

surface molecules on endothelial cells. Once bound, the leukocytes migrate across the blood vessel wall to enter the injured site and release chemical mediators to combat infection. For reviews of adhesion receptors of the immune system, *see*, for example, Springer³ and Osborn⁴.

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Inflammatory brain disorders, such as experimental autoimmune encephalomyelitis (EAE), multiple sclerosis (MS) and meningitis, are examples of central nervous system disorders in which the endothelium/leukocyte adhesion mechanism results in destruction to otherwise healthy brain tissue. Large numbers of leukocytes migrate across the blood brain barrier (BBB) in subjects with these inflammatory diseases. The leukocytes release toxic mediators that cause extensive tissue damage resulting in impaired nerve conduction and paralysis.

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In other organ systems, tissue damage also occurs via an adhesion mechanism resulting in migration or activation of leukocytes. For example, it has been shown that the initial insult following myocardial ischemia to heart tissue can be further complicated by leukocyte entry to the injured tissue causing still further insult (Vedder et al.⁵). Other inflammatory conditions mediated by an adhesion mechanism include, by way of example, asthma⁶⁻⁸, Alzheimer's disease, atherosclerosis⁹⁻¹⁰, AIDS dementia¹¹, diabetes¹²⁻¹⁴ (including acute juvenile onset diabetes), inflammatory bowel disease¹⁵ (including ulcerative colitis and Crohn's disease), multiple sclerosis¹⁶⁻¹⁷, rheumatoid arthritis¹⁸⁻²¹, tissue transplantation²², tumor metastasis²³⁻²⁸, meningitis, encephalitis, stroke, and other cerebral traumas, nephritis, retinitis, atopic dermatitis, psoriasis, myocardial ischemia and acute leukocyte-mediated lung injury such as that which occurs in adult respiratory distress syndrome.

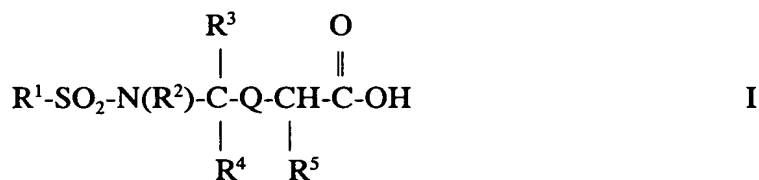
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In view of the above, assays for determining the VLA-4 level in a biological sample containing VLA-4 would be useful, for example, to diagnosis VLA-4 mediated conditions. Additionally, despite these advances in the understanding of leukocyte adhesion, the art has only recently addressed the use of inhibitors of adhesion in the treatment of inflammatory brain diseases and other inflammatory conditions^{29,30}. The present invention addresses these and other needs.

SUMMARY OF THE INVENTION

This invention provides compounds which bind to VLA-4. Such compounds can be used, for example, to assay for the presence of VLA-4 in a sample and in pharmaceutical compositions to inhibit cellular adhesion mediated by VLA-4, for example, binding of VCAM-1 to VLA-4. The compounds of this invention have a binding affinity to VLA-4 as expressed by an IC₅₀ of about 15 μ M or less (as measured by Example 56 below) which compounds are defined by formula I below:



where

R¹ is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl;

5 R² is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and R¹ and R² together with the nitrogen atom bound to R² and the SO₂ group bound to R¹ can form a heterocyclic or a substituted heterocyclic group;

10 R³ is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and, when R² does not form a heterocyclic group with R¹, R² and R³ together with the nitrogen atom bound to R² and the carbon atom bound to R³ can form a heterocyclic or a substituted heterocyclic group;

15 R⁴ is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and, when R³ does not form a heterocyclic group with R², then R³ and R⁴ together with the carbon atom to which they are attached can form a cycloalkyl, substituted cycloalkyl, heterocyclic or substituted heterocyclic group;

20 R⁵ is selected from the group consisting of isopropyl, -CH₂X and =CH-X where X is selected from the group consisting of hydrogen, hydroxyl, acylamino, alkyl, alkoxy, aryloxy, aryl, aryloxyaryl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted alkyl, substituted alkoxy, substituted aryl, substituted aryloxy, substituted aryloxyaryl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic with the proviso that when R⁵ is =CH-X then (H) is removed from the formula and X is not hydroxyl;

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Q is $-C(X)NR^7$ - wherein R^7 is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur;

and pharmaceutically acceptable salts thereof

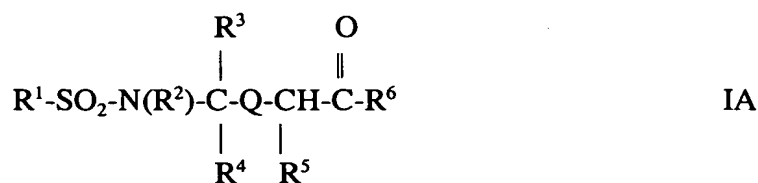
5 with the provisos that

A. when R^1 and R^2 are joined together with the SO_2 and nitrogen atom to which they are attached respectively to form a benzoisothiazolone heterocyclic ring, R^3 is methyl, R^4 is methyl and Q is $-C(O)NH-$ then R^5 is not benzyl;

10 B. when R^1 is *p*-methylphenyl, R^2 is hydrogen, R^3 and R^4 are joined together with the carbon atom to which they are joined to form cyclohexyl, Q is $-C(O)NH-$, then R^5 is not benzyl; and

C. when R^1 is *p*-methylphenyl, R^2 is methyl, R^3 and R^4 are joined together with the carbon atom to which they are joined to form cyclopentyl, 15 Q is $-C(O)N(CH_3)-$, then R^5 is not benzyl.

In another embodiment, the compounds of this invention can also be provided as prodrugs which convert (e.g., hydrolyze, metabolize, etc.) *in vivo* to a compound of formula I above. In a preferred example of such an 20 embodiment, the carboxylic acid in the compound of formula I is modified into a group which, *in vivo*, will convert to the carboxylic acid (including salts thereof). In a particularly preferred embodiment, such prodrugs are represented by compounds of formula IA:



where

R² is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and R¹ and R² together with the nitrogen atom bound to R² and the SO₂ group bound to R¹ can form a heterocyclic or a substituted heterocyclic group;

10 R^3 is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and, when R^2 does not form a heterocyclic group with R^1 , R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 can form a
15 heterocyclic or a substituted heterocyclic group;

R⁴ is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and, when R³ does not form a heterocyclic group with R², then R³ and R⁴ together with the carbon atom to which they are attached can form a cycloalkyl, substituted cycloalkyl, heterocyclic or substituted heterocyclic group;

R⁵ is selected from the group consisting of isopropyl, -CH₂X and =CH-X where X is selected from the group consisting of hydrogen, hydroxyl, acylamino, alkyl, alkoxy, aryloxy, aryl, aryloxyaryl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted alkyl, substituted alkoxy, substituted aryl, substituted aryloxy, substituted aryloxyaryl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and

substituted heterocyclic with the proviso that when R^5 is $=CH-X$ then (H) is removed from the formula and X is not hydroxyl;

R^6 is selected from the group consisting of 2,4-dioxo-tetrahydrofuran-3-yl (3,4-enol), amino, alkoxy, substituted alkoxy, cycloalkoxy, substituted cycloalkoxy, -O-(N-succinimidyl), -NH-adamantyl, -O-cholest-5-en-3- β -yl, -NHOY where Y is hydrogen, alkyl, substituted alkyl, aryl, and substituted aryl, $-NH(CH_2)_pCOOY$ where p is an integer of from 1 to 8 and Y is as defined above, $-OCH_2NR^9R^{10}$ where R^9 is selected from the group consisting of -C(O)-aryl and -C(O)-substituted aryl and R^{10} is selected from the group consisting of hydrogen and $-CH_2COOR^{11}$ where R^{11} is alkyl, and $-NHOSO_2Z$ where Z is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

Q is $-C(X)NR^7-$ wherein R^7 is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur;

and pharmaceutically acceptable salts thereof
with the following provisos

A. when R^1 is *o*-carboxymethylphenyl, R^2 is hydrogen, R^3 is methyl, R^4 is methyl, R^5 is benzyl and Q is $-C(O)NH-$, then R^6 is not -O-benzyl;

B. when R^1 and R^2 are joined to form a benzoisothiazolone heterocyclic ring, R^3 is methyl, R^4 is methyl, R^5 is benzyl and Q is $-C(O)NH-$, then R^6 is not -O-benzyl;

C. when R^1 is *p*-methylphenyl, R^2 is methyl, R^3 and R^4 are joined together with the carbon atom to which they are joined to form cyclopentyl or cyclohexyl, R^5 is benzyl and Q is $-C(O)NH-$, then R^6 is not ethoxy;

D. when R^1 is benzyl, R^2 , R^3 and R^4 are methyl, R^5 is *p*-hydroxybenzyl and Q is $-C(O)NH-$, then R^6 is not *t*-butoxy;

E. when R¹ is *p*-methylphenyl, R² is methyl, R³ and R⁴ are joined together with the carbon atom to which they are joined to form cyclopentyl or cyclohexyl, R⁵ is *p*-[*N,N*-(dimethylamino)carbonyloxy]benzyl and Q is -C(O)NH-, then R⁶ is not *t*-butoxy;

5 F. when R¹ is benzyl, R², R³ and R⁴ are methyl, R⁵ is *p*-[*N,N*-(dimethylamino)carbonyloxy]benzyl and Q is -C(O)NH-, then R⁶ is not *t*-butoxy; and

10 G. when R¹ is *p*-methylphenyl, R² and R³ are joined together with the nitrogen atom pendent to R² and the carbon atom pendent to R³ to form a pyrrolidinyl ring, R⁴ is methyl, R⁵ is *p*-hydroxybenzyl then R⁶ is not *t*-butoxy.

Preferably, in the compounds of formula I and IA above, R¹ is selected from the group consisting of alkyl, substituted alkyl, aryl,
15 substituted aryl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl. Even more preferably R¹ is selected from the group consisting of 4-methylphenyl, methyl, benzyl, *n*-butyl, 4-chlorophenyl, 1-naphthyl, 2-naphthyl, 4-methoxyphenyl, phenyl, 2,4,6-trimethylphenyl, 2-(methoxycarbonyl)phenyl, 2-carboxyphenyl, 3,5-dichlorophenyl, 4-
20 trifluoromethylphenyl, 3,4-dichlorophenyl, 3,4-dimethoxyphenyl, 4-(CH₃C(O)NH-)phenyl, 4-trifluoromethoxyphenyl, 4-cyanophenyl, isopropyl, 3,5-di-(trifluoromethyl)phenyl, 4-*t*-butylphenyl, 4-*t*-butoxyphenyl, 4-nitrophenyl, 2-thienyl, 1-N-methyl-3-methyl-5-chloropyrazol-4-yl, phenethyl, 1-N-methylimidazol-4-yl, 4-bromophenyl, 4-amidinophenyl, 4-
25 methylamidinophenyl, 4-[CH₃SC(=NH)]phenyl, 5-chloro-2-thienyl, 2,5-dichloro-4-thienyl, 1-N-methyl-4-pyrazolyl, 2-thiazolyl, 5-methyl-1,3,4-thiadiazol-2-yl, 4-[H₂NC(S)]phenyl, 4-aminophenyl, 4-fluorophenyl, 2-fluorophenyl, 3-fluorophenyl, 3,5-difluorophenyl, pyridin-3-yl, pyrimidin-2-yl, 4-(3'-dimethylamino-*n*-propoxy)-phenyl, and 1-methylpyrazol-4-yl.

Preferably, in the compounds of formula I and IA above, R² is hydrogen, methyl, phenyl, benzyl, -(CH₂)₂-2-thienyl, and -(CH₂)₂-φ.

5 In one embodiment, R¹ and R² together with the nitrogen atom bound to R² and the SO₂ group bound to R¹ are joined to form a heterocyclic group or substituted heterocyclic group. Preferred heterocyclic and substituted heterocyclic groups include those having from 5 to 7 ring atoms having 2 to 3 heteroatoms in the ring selected from nitrogen, oxygen and sulfur which ring is optionally fused to another ring such as a phenyl or cyclohexyl ring to
10 provide for a fused ring heterocycle of from 10 to 14 ring atoms having 2 to 4 heteroatoms in the ring selected from nitrogen, oxygen and sulfur. Specifically preferred R¹/R² joined groups include, by way of example, benzisothiazolonyl (saccharin-2-yl).

15 In one preferred embodiment, R² and R³ together with the nitrogen atom bound to R² substituent and the carbon bound to the R³ substituent form a heterocyclic group or a substituted heterocyclic group of 4 to 6 ring atoms having 1 to 2 heteroatoms in the ring selected from nitrogen, oxygen and sulfur which ring is optionally substituted with 1 to 2 substituents selected
20 from fluoro, methyl, hydroxy, amino, phenyl, thiophenyl, thiobenzyl or can be fused to another ring such as a phenyl or cycloalkyl ring to provide for a fused ring heterocycle of from 10 to 14 ring atoms having 1 to 2 heteroatoms in the ring selected from nitrogen, oxygen and sulfur. Such heterocyclic rings include azetidiny (e.g., L-azetidiny), thiazolidiny (e.g., L-
25 thiazolidiny), piperidiny (e.g., L-piperidiny), piperiziny (e.g., L-piperiziny), dihydroindolyl (e.g., L-2,3-dihydroindol-2-yl), tetrahydroquinoliny (e.g., L-1,2,3,4-tetrahydroquinolin-2-yl), thiomorpholiny (e.g., L-thiomorpholin-3-yl), pyrrolidiny (e.g., L-pyrrolidiny), substituted pyrrolidiny such as
30 4-hydroxypyrrolidiny (e.g., 4-α-(or β)-hydroxy-L-pyrrolidiny),

- 4-fluoropyrrolidinyl (e.g., 4- α -(or β)-fluoro-L-pyrrolidinyl),
3-phenylpyrrolidinyl (e.g., 3- α -(or β)-phenyl-L-pyrrolidinyl),
3-thiophenylpyrrolidinyl (e.g., 3- α -(or β)-thiophenyl-L-pyrrolidinyl),
4-aminopyrrolidinyl (e.g., 4- α -(or β)-amino-L-pyrrolidinyl),
5 3-methoxypyrrolidinyl (e.g., 3- α -(or β)-methoxy-L-pyrrolidinyl),
4,4-dimethylpyrrolidinyl, substituted piperizinyl such as 4-N-Cbz-
piperizinyl, substituted thiazolidinyl such as 5,5-dimethylthiazolidin-4-yl,
1,1-dioxo-thiazolidinyl (e.g., L-1,1-dioxo-thiazolidin-2-yl), substituted
1,1-dioxo-thiazolidinyl such as L-1,1-dioxo-5,5-dimethylthiazolidin-2-yl,
10 1,1-dioxothiophoridinyl (e.g., L-1,1-dioxo-thiophoridin-3-yl) and the
like.

- Preferably, in the compounds of formula I and IA above, R³ includes
all of the isomers arising by substitution with methyl, phenyl, benzyl,
15 diphenylmethyl, -CH₂CH₂-COOH, -CH₂-COOH, 2-amidoethyl, *iso*-butyl, *t*-
butyl, -CH₂O-benzyl and hydroxymethyl. Additionally, in another preferred
embodiment, R³ and R² together with the nitrogen atom bound to R² can
form a heterocyclic group or substituted heterocyclic group.

- 20 Preferably, in the compounds of formula I and IA above, R⁴ is
selected from the group consisting of methyl, ethyl, phenyl and where R³ and
R⁴ are joined together with the carbon atom to which they are attached to
form a cycloalkyl group of from 3 to 6 carbon atoms or a heterocyclic group
of from 3 to 8 ring atoms. Preferred cycloalkyl alkyl groups include
25 cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Q is preferably -C(O)NH- or -C(S)NH-.

- R^5 is preferably selected from all possible isomers arising by substitution with the following groups: 4-methylbenzyl, 4-hydroxybenzyl, 4-methoxybenzyl, 4-*t*-butoxybenzyl, 4-benzyloxybenzyl, 4-[ϕ -CH(CH₃)O-]benzyl, 4-[ϕ -CH(COOH)O-]benzyl, 4-
- 5 [BocNHCH₂C(O)NH-]benzyl, 4-chlorobenzyl, 4-[NH₂CH₂C(O)NH-]benzyl, 4-carboxybenzyl, 4-[CbzNHCH₂CH₂NH-]benzyl, 3-hydroxy-4-(ϕ -OC(O)NH-)benzyl, 4-[HOOCCH₂CH₂C(O)NH-]benzyl, benzyl, 4-[2'-carboxylphenoxy-]benzyl, 4-[ϕ -C(O)NH-]benzyl, 3-carboxybenzyl, 4-iodobenzyl, 4-hydroxy-3,5-diiodobenzyl, 4-hydroxy-3-iodobenzyl, 4-[2'-
- 10 carboxyphenyl-]benzyl, ϕ -CH₂CH₂-, 4-nitrobenzyl, 2-carboxybenzyl, 4-[dibenzylamino]-benzyl, 4-[(1'-cyclopropylpiperidin-4'-yl)-C(O)NH-]benzyl, 4-[NHC(O)CH₂NHBoc]benzyl, 4-carboxybenzyl, 4-hydroxy-3-nitrobenzyl, 4-[NHC(O)CH(CH₃)NHBoc]benzyl, 4-[NHC(O)CH(CH₂ ϕ)NHBoc]-benzyl, isobutyl, methyl, 4-[CH₃C(O)NH-]benzyl, -CH₂-(3-indolyl),
- 15 *n*-butyl, *t*-butyl-OC(O)CH₂-, *t*-butyl-OC(O)CH₂CH₂-, H₂NC(O)CH₂-, H₂NC(O)CH₂CH₂-, BocNH-(CH₂)₄-, *t*-butyl-OC(O)-(CH₂)₂-, HOOCCH₂-, HOOC(CH₂)₂-, H₂N(CH₂)₄-, isopropyl, (1-naphthyl)-CH₂-, (2-naphthyl)-CH₂-, (2-thiophenyl)-CH₂-, (ϕ -CH₂-OC(O)NH-(CH₂)₄-, cyclohexyl-CH₂-, benzyloxy-CH₂-, HOCH₂-, 5-(3-N-benzyl)imidazolyl-CH₂-, 2-pyridyl-CH₂-,
- 20 3-pyridyl-CH₂-, 4-pyridyl-CH₂-, 5-(3-N-methyl)imidazolyl-CH₂-, N-benzylpiperid-4-yl-CH₂-, N-Boc-piperidin-4-yl-CH₂-, N-(phenyl-carbonyl)piperidin-4-yl-CH₂-, H₃CSCH₂CH₂-, 1-N-benzylimidazol-4-yl-CH₂-, *iso*-propyl-C(O)NH-(CH₂)₄-, *iso*-butyl-C(O)NH-(CH₂)₄-, phenyl-C(O)NH-(CH₂)₄-, benzyl-C(O)NH-(CH₂)₄-, allyl-C(O)NH-(CH₂)₄-, 4-(3-N-
- 25 methylimidazolyl)-CH₂-, 4-imidazolyl, 4-[(CH₃)₂NCH₂CH₂CH₂-O-]benzyl, 4-[(benzyl)₂N-]benzyl, 4-aminobenzyl, allyloxy-C(O)NH(CH₂)₄-, allyloxy-C(O)NH(CH₂)₃-, allyloxy-C(O)NH(CH₂)₂-, NH₂C(O)CH₂-, ϕ -CH=, 2-pyridyl-C(O)NH-(CH₂)₄-, 4-methylpyrid-3-yl-C(O)NH-(CH₂)₄-, 3-methylthien-2-yl-C(O)NH-(CH₂)₄-, 2-pyrrolyl-C(O)NH-(CH₂)₄-, 2-furanyl-
- 30 C(O)NH-(CH₂)₄-, 4-methylphenyl-SO₂-N(CH₃)CH₂C(O)NH(CH₂)₄-, 4-

- [cyclopentylacetylenyl]-benzyl, 4-[-NHC(O)-(N-Boc)-pyrrolidin-2-yl]-benzyl-, 1-N-methylimidazol-4-yl-CH₂-, 1-N-methylimidazol-5-yl-CH₂-, imidazol-5-yl-CH₂-, 6-methylpyrid-3-yl-C(O)NH-(CH₂)₄-, 4-[2'-carboxymethylphenyl]-benzyl, 4-[-NHC(O)NHCH₂CH₂CH₂-φ]-benzyl,
- 5 4-[-NHC(O)NHCH₂CH₂-φ]-benzyl, -CH₂C(O)NH(CH₂)₄φ, 4-[φ(CH₂)₄O]-benzyl, 4-[-C≡C-φ-4'φ]-benzyl, 4-[-C≡C-CH₂-O-S(O)₂-4'-CH₃-φ]-benzyl, 4-[-C≡C-CH₂NHC(O)NH₂]-benzyl, 4-[-C≡C-CH₂-O-4'-COOCH₂CH₃-φ]-benzyl, 4-[-C≡C-CH(NH₂)-cyclohexyl]-benzyl,
- 10 -(CH₂)₄NHC(O)CH₂-3-indolyl, -(CH₂)₄NHC(O)CH₂CH₂-3-indolyl, -(CH₂)₄NHC(O)-3-(5-methoxyindolyl), -(CH₂)₄NHC(O)-3-(1-methylindolyl), -(CH₂)₄NHC(O)-4-(-SO₂(CH₃)-φ), -(CH₂)₄NHC(O)-4-(C(O)CH₃)-phenyl, -(CH₂)₄NHC(O)-4-fluorophenyl, -(CH₂)₄NHC(O)CH₂O-4-fluorophenyl, 4-[-C≡C-(2-pyridyl)]-benzyl, 4-[-C≡C-CH₂-O-phenyl]-benzyl, 4-[-C≡C-CH₂OCH₃]-benzyl, 4-[-C≡C-(3-hydroxyphenyl)]-benzyl,
- 15 4-[-C≡C-CH₂-O-4'-(-C(O)OC₂H₅)phenyl]-benzyl, 4-[-C≡C-CH₂CH(C(O)OCH₃)₂]-benzyl, 4-[-C≡C-CH₂NH-(4,5-dihydro-4-oxo-5-phenyl-oxazol-2-yl)], 3-aminobenzyl, 4-[-C≡C-CH₂CH(NHC(O)CH₃)C(O)OH]-benzyl, methyl, -CH₂C(O)NHCH(CH₃)φ, -CH₂C(O)NHCH₂-(4-dimethylamino)-φ,
- 20 -CH₂C(O)NHCH₂-4-nitrophenyl, -CH₂CH₂C(O)N(CH₃)CH₂-φ, -CH₂CH₂C(O)NHCH₂CH₂-(N-methyl)-2-pyrrolyl, -CH₂CH₂C(O)NHCH₂CH₂CH₂CH₃, -CH₂CH₂C(O)NHCH₂CH₂-3-indolyl, -CH₂C(O)N(CH₃)CH₂phenyl, -CH₂C(O)NH(CH₂)₂-(N-methyl)-2-pyrrolyl, -CH₂C(O)NHCH₂CH₂CH₂CH₃, -CH₂C(O)NHCH₂CH₂-3-indolyl,
- 25 -(CH₂)₂C(O)NHCH(CH₃)φ, -(CH₂)₂C(O)NHCH₂-4-dimethylaminophenyl, -(CH₂)₂C(O)NHCH₂-4-nitrophenyl, -CH₂C(O)NH-4-[-NHC(O)CH₃-phenyl], -CH₂C(O)NH-4-pyridyl, -CH₂C(O)NH-4-[dimethylaminophenyl], -CH₂C(O)NH-3-methoxyphenyl, -CH₂CH₂C(O)NH-4-chlorophenyl, -CH₂CH₂C(O)NH-2-pyridyl, -CH₂CH₂C(O)NH-4-methoxyphenyl,
- 30 -CH₂CH₂C(O)NH-3-pyridyl, 4-[(CH₃)₂NCH₂CH₂O]-benzyl,

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- (CH₂)₃NHC(NH)NH-SO₂-4-methylphenyl, 4-[(CH₃)₂NCH₂CH₂O]-benzyl,
 -(CH₂)₄NHC(O)NHCH₂CH₃, -(CH₂)₄NHC(O)NH-phenyl,
 -(CH₂)₄NHC(O)NH-4-methoxyphenyl, 4-[4'-pyridyl-C(O)NH]-benzyl,
 4-[3'-pyridyl-C(O)NH]-benzyl, 4-[-NHC(O)NH-3'-methylphenyl]-benzyl,
 5 4-[-NHC(O)CH₂NHC(O)NH-3'-methylphenyl]-benzyl, 4-[-NHC(O)-(2',3'-
 dihydroindol-2-yl)]-benzyl, 4-[-NHC(O)-(2',3'-dihydro-N-Boc-indol-2-yl)]-
 benzyl, p-[-OCH₂CH₂-1'-(4'-pyrimidinyl)-piperazinyl]-benzyl,
 4-[-OCH₂CH₂-(1'-piperidinyl)-benzyl, 4-[-OCH₂CH₂-(1'-pyrrolidinyl)]-
 benzyl, 4-[-OCH₂CH₂CH₂-(1'-piperidinyl)]-benzyl-, -CH₂-3-(1,2,4-triazolyl),
 10 4-[-OCH₂CH₂CH₂-4-(3'-chlorophenyl)-piperazin-1-yl]-benzyl,
 4-[-OCH₂CH₂N(φ)CH₂CH₃]-benzyl, 4-[-OCH₂-3'-(N-Boc)-piperidinyl]-
 benzyl, 4-[di-*n*-pentylamino]-benzyl, 4-[*n*-pentylamino]-benzyl, 4-[di-*iso*-
 propylamino-CH₂CH₂O]-benzyl, 4-[-OCH₂CH₂-(N-morpholinyl)]-benzyl, 4-
 [-O-(3'-(N-Boc)-piperidinyl)-benzyl, 4-[-OCH₂CH(NHBoc)CH₂cyclohexyl]-
 15 benzyl, *p*-[OCH₂CH₂-(N-piperidinyl)-benzyl, 4-[-OCH₂CH₂CH₂-(4-*m*-
 chlorophenyl)-piperazin-1-yl]-benzyl, 4-[-OCH₂CH₂-(N-homopiperidinyl)-
 benzyl, 4-[-NHC(O)-3'-(N-Boc)-piperidinyl]-benzyl, 4-[-
 OCH₂CH₂N(benzyl)₂]-benzyl, -CH₂-2-thiazolyl, 3-hydroxybenzyl,
 4-[-OCH₂CH₂CH₂N(CH₃)₂]-benzyl, 4-[-NHC(S)NHCH₂CH₂-(N-
 20 morpholino)]-benzyl, 4-[-OCH₂CH₂N(C₂H₅)₂]-benzyl,
 4-[-OCH₂CH₂CH₂N(C₂H₅)₂]-benzyl, 4-[CH₃(CH₂)₄NH]-benzyl, 4-[N-*n*-
 butyl,N-*n*-pentylamino]-benzyl, 4-[-NHC(O)-4'-piperidinyl]benzyl,
 4-[-NHC(O)CH(NHBoc)(CH₂)₄NHCbz]-benzyl, 4-[-NHC(O)-(1',2',3',4'-
 tetrahydro-N-Boc-isoquinolin-1'-yl)]-benzyl,
 25 p-[-OCH₂CH₂CH₂-1'-(4'-methyl)-piperazinyl]-benzyl, -(CH₂)₄NH-Boc,
 3-[-OCH₂CH₂CH₂N(CH₃)₂]-benzyl, 4-[-OCH₂CH₂CH₂N(CH₃)₂]-benzyl, 3-[-
 OCH₂CH₂-(1'-pyrrolidinyl)]-benzyl, 4-[-OCH₂CH₂CH₂N(CH₃)benzyl]-
 benzyl, 4-[-NHC(S)NHCH₂CH₂CH₂-(N-morpholino)]-benzyl,
 4-[-OCH₂CH₂-(N-morpholino)]-benzyl, 4-[-NHCH₂-(4'-chlorophenyl)]-
 30 benzyl, 4-[-NHC(O)NH-(4'-cyanophenyl)]-benzyl, 4-[-OCH₂COOH]-benzyl,

- 4-[-OCH₂COO-*t*-butyl]-benzyl, 4-[-NHC(O)-5'-fluoroindol-2-yl]-benzyl, 4-[-NHC(S)NH(CH₂)₂-1-piperidiny]-benzyl,
4-[-N(SO₂CH₃)(CH₂)₃-N(CH₃)₂]-benzyl, 4-[-NHC(O)CH₂CH(C(O)OCH₂φ)-NHCbz]-benzyl, 4-[-NHS(O)₂CF₃]-benzyl, 3-[-O-(N-methylpiperidin-4'-yl)-benzyl, 4-[-C(=NH)NH₂]-benzyl, 4-[-NHSO₂-CH₂Cl]-benzyl,
4-[-NHC(O)-(1',2',3',4'-tetrahydroisoquinolin-2'-yl)-benzyl,
4-[-NHC(S)NH(CH₂)₃-N-morpholino]-benzyl,
4-[-NHC(O)CH(CH₂CH₂CH₂CH₂NH₂)NHBoc]-benzyl, 4-[-C(O)NH₂]-benzyl, 4-[-NHC(O)NH-3'-methoxyphenyl]-benzyl,
4-[-OCH₂CH₂-indol-3'-yl]-benzyl, 4-[-OCH₂C(O)NH-benzyl]-benzyl,
4-[-OCH₂C(O)O-benzyl]-benzyl, 4-[-OCH₂C(O)OH]-benzyl,
4-[-OCH₂-2'-(4',5'-dihydro)imidazolyl]-benzyl,
-CH₂C(O)NHCH₂-(4-dimethylamino)phenyl, -CH₂C(O)NHCH₂-(4-dimethylamino)phenyl, 4-[-NHC(O)-L-2'-pyrrolidiny-N-SO₂-4'-methylphenyl]-benzyl, 4-[-NHC(O)NHCH₂CH₂CH₃]-benzyl, 4-aminobenzyl]-benzyl, 4-[-OCH₂CH₂-1-(4-hydroxy-4-(3-methoxypyrrol-2-yl)-piperazinyl]-benzyl, 4-[-O-(N-methylpiperidin-4'-yl)]-benzyl,
3-methoxybenzyl, 4-[-NHC(O)-piperidin-3'-yl]-benzyl, 4-[-NHC(O)-pyridin-2'-yl]-benzyl, 4-[-NHCH₂-(4'-chlorophenyl)]-benzyl,
4-[-NHC(O)-(N-(4'-CH₃-φ-SO₂)-L-pyrrolidin-2'-yl)]-benzyl,
4-[-NHC(O)NHCH₂CH₂-φ]-benzyl, 4-[-OCH₂C(O)NH₂]-benzyl,
4-[-OCH₂C(O)NH-*t*-butyl]-benzyl, 4-[-OCH₂CH₂-1-(4-hydroxy-4-phenyl)-piperidiny]-benzyl, 4-[-NHSO₂-CH=CH₂]-benzyl,
4-[-NHSO₂-CH₂CH₂Cl]-benzyl, -CH₂C(O)NHCH₂CH₂N(CH₃)₂, 4-[(1'-Cbz-piperidin-4'-yl)C(O)NH-]benzyl, 4-[(1'-Boc-piperidin-4'-yl)C(O)NH-]benzyl, 4-[(2'-bromophenyl)C(O)NH-]benzyl, 4-[-NHC(O)-pyridin-4'-yl]-benzyl, 4-[(4'-(CH₃)₂NC(O)O-)phenyl]-C(O)NH-]benzyl,
4-[-NHC(O)-1'-methylpiperidin-4'-yl]-benzyl, 4-(dimethylamino)benzyl,

- 4-[-NHC(O)-(1'-N-Boc)-piperidin-2'-yl]-benzyl, 3-[-NHC(O)-pyridin-4'-yl]-benzyl, 4-[(*tert*-butyl-O(O)CCH₂-O-benzyl)-NH-]benzyl, [BocNHCH₂C(O)NH-]butyl, 4-benzyl-benzyl, 2-hydroxyethyl, 4-[(Et)₂NCH₂CH₂CH₂NHC(S)NH-]benzyl, 4-[(1'-Boc-4'-hydroxypyrrolidin-2'-yl)C(O)NH-]benzyl, 4-[ϕ CH₂CH₂CH₂NHC(S)NH-]benzyl, 4-[(perhydroindolin-2'-yl)C(O)NH-]benzyl, 2-[4-hydroxy-4-(3-methoxythien-2-yl)piperidin-1-yl]ethyl, 4-[(1'-Boc-perhydroindolin-2'-yl)-C(O)NH-]benzyl, 4-[*N*-3-methylbutyl-*N*-trifluoromethanesulfonyl]amino]-benzyl, 4-[*N*-vinylsulfonyl]amino]benzyl-, 4-[2-(2-azabicyclo[3.2.2]octan-2-yl)ethyl-O-]benzyl, 4-[4'-hydroxypyrrolidin-2'-yl)C(O)NH-]benzyl, 4-(ϕ NHC(S)NH)benzyl, 4-(EtNHC(S)NH)benzyl, 4-(ϕ CH₂NHC(S)NH)benzyl, 3-[(1'-Boc-piperidin-2'-yl)C(O)NH-]benzyl, 3-[piperidin-2'-yl-C(O)NH-]benzyl, 4-[(3'-Boc-thiazolidin-4'-yl)C(O)NH-]benzyl, 4-(pyridin-3'-yl-NHC(S)NH)benzyl, 4-(CH₃-NHC(S)NH)benzyl-, 4-(H₂NCH₂CH₂CH₂C(O)NH)benzyl, 4-(BocHNCH₂CH₂CH₂C(O)NH)benzyl, 4-(pyridin-4'-yl-CH₂NH)benzyl, 4-[(*N,N*-di(4-*N,N*-dimethylamino)benzyl)amino]benzyl, 4-[(1-Cbz-piperidin-4-yl)C(O)NH-]butyl, 4-[ϕ CH₂OCH₂(BocHN)CHC(O)NH]benzyl, 4-[(piperidin-4'-yl)C(O)NH-]benzyl, 4-[(pyrrolidin-2'-yl)C(O)NH-]benzyl, 4-(pyridin-3'-yl-C(O)NH)butyl, 4-(pyridin-4'-yl-C(O)NH)butyl, 4-(pyridin-3'-yl-C(O)NH)benzyl, 4-[CH₃NHCH₂CH₂CH₂C(O)NH-]benzyl, 4-[CH₃N(Boc)CH₂CH₂CH₂C(O)NH-]benzyl, 4-(aminomethyl)benzyl, 4-[ϕ CH₂OCH₂(H₂N)CHC(O)NH]benzyl, 4-[(1',4'-di(Boc)piperazin-2'-yl)-C(O)NH-]benzyl, 4-[(piperazin-2'-yl)-C(O)NH-]benzyl, 4-[(*N*-toluenesulfonylpyrrolidin-2'-yl)C(O)NH-]butyl, 4-[-NHC(O)-4'-piperidinyl]butyl, 4-[-NHC(O)-1'-N-Boc-piperidin-2'-yl]-benzyl, 4-[-NHC(O)-piperidin-2'-yl]-benzyl, 4-[(1'-N-Boc-2',3'-dihydroindolin-2'-yl)-C(O)NH-]benzyl, 4-(pyridin-3'-yl-CH₂NH)benzyl, 4-[(1'-Cbz-piperidin-4'-yl)C(O)NH-]benzyl, 4-[(piperidin-1'-yl)C(O)CH₂-O-]benzyl, 4-[(CH₃)₂CH)₂NC(O)CH₂-O-]benzyl, 4-[HO(O)C(Cbz-NH)CHCH₂CH₂-

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C(O)NH-]benzyl, 4-[ϕ CH₂O(O)C(Cbz-NH)CHCH₂CH₂-C(O)NH-]benzyl, 4-[-NHC(O)-2'-methoxyphenyl]-benzyl, 4-[(pyrazin-2'-yl)C(O)NH-]benzyl, 4-[HO(O)C(NH₂)CHCH₂CH₂-C(O)NH-]benzyl, 4-(2'-formyl-1',2',3',4'-tetrahydroisoquinolin-3'-yl-CH₂NH-)benzyl, *N*-Cbz-NHCH₂-,

5 4-[(4'-methylpiperazin-1'-yl)C(O)O-]benzyl, 4-[CH₃(*N*-Boc)NCH₂C(O)NH-]benzyl, 4-[-NHC(O)-(1',2',3',4'-tetrahydro-*N*-Boc-isoquinolin-3'-yl)-]benzyl, 4-[CH₃NHCH₂C(O)NH-]benzyl, (CH₃)₂NC(O)CH₂-, 4-(*N*-methylacetamido)benzyl, 4-(1',2',3',4'-tetrahydroisoquinolin-3'-yl-CH₂NH-)benzyl, 4-

10 [(CH₃)₂NHCH₂C(O)NH-]benzyl, (1-toluenesulfonylimidizol-4-yl)methyl, 4-[(1'-Boc-piperidin-4'-yl)C(O)NH-]benzyl, 4-trifluoromethylbenzyl, 4-[(2'-bromophenyl)C(O)NH-]benzyl, 4-[(CH₃)₂NC(O)NH-]benzyl, 4-[CH₃OC(O)NH-]benzyl, 4-[(CH₃)₂NC(O)O-]benzyl, 4-[(CH₃)₂NC(O)N(CH₃)-]benzyl, 4-[CH₃OC(O)N(CH₃)-]benzyl,

15 4-(*N*-methyltrifluoroacetamido)benzyl, 4-[(1'-methoxycarbonylpiperidin-4'-yl)C(O)NH-]benzyl, 4-[(4'-phenylpiperidin-4'-yl)C(O)NH-]benzyl, 4-[(4'-phenyl-1'-Boc-piperidin-4'-yl)-C(O)NH-]benzyl, 4-[(piperidin-4'-yl)C(O)O-]benzyl, 4-[(1'-methylpiperidin-4'-yl)-O-]benzyl, 4-[(1'-methylpiperidin-4'-yl)C(O)O-]benzyl, 4-[(4'-methylpiperazin-1'-yl)C(O)NH-]benzyl, 3-[(CH₃)₂NC(O)O-]benzyl, 4-[(4'-phenyl-1'-Boc-piperidin-4'-yl)-C(O)O-]benzyl, 4-(*N*-toluenesulfonylamino)benzyl, 4-[(CH₃)₃CC(O)NH-]benzyl, 4-[(morpholin-4'-yl)C(O)NH-]benzyl, 4-[(CH₃CH₂)₂NC(O)NH-]benzyl, 4-[-C(O)NH-(4'-piperidiny)]benzyl, 4-[(2'-trifluoromethylphenyl)C(O)NH-]benzyl, 4-[(2'-methylphenyl)C(O)NH-]benzyl, 4-[(CH₃)₂NS(O)₂O-]benzyl,

25 4-[(pyrrolidin-2'-yl)C(O)NH-]benzyl, 4-[-NHC(O)-piperidin-1'-yl]benzyl, 4-[(thiomorpholin-4'-yl)C(O)NH-]benzyl, 4-[(thiomorpholin-4'-yl sulfone)-C(O)NH-]benzyl, 4-[(morpholin-4'-yl)C(O)O-]benzyl, 3-nitro-4-(CH₃OC(O)CH₂O-)benzyl, (2-benzoxazolinon-6-yl)methyl-,

30 (2*H*-1,4-benzoxazin-3(4*H*)-one-7-yl)methyl-, 4-[(CH₃)₂NS(O)₂NH-]benzyl,

4-[(CH₃)₂NS(O)₂N(CH₃)-]benzyl, 4-[(thiomorpholin-4'-yl)C(O)O-]benzyl,
 4-[(thiomorpholin-4'-yl sulfone)-C(O)O-]benzyl,
 4-[(piperidin-1'-yl)C(O)O-]benzyl, 4-[(pyrrolidin-1'-yl)C(O)O-]benzyl,
 4-[(4'-methylpiperazin-1'-yl)C(O)O-]benzyl, 4-[(2'-methylpyrrolidin-1'-yl)-,
 5 (pyridin-4-yl)methyl-, 4-[(piperazin-4'-yl)-C(O)O-]benzyl,
 4-[(1'-Boc-piperazin-4'-yl)-C(O)O-]benzyl, 4-[(4'-acetylpiperazin-1'-
 yl)C(O)O-]benzyl, *p*-[(4'-methanesulfonylpiperazin-1'-yl)-benzyl, 3-nitro-4-
 [(morpholin-4'-yl)-C(O)O-]benzyl, 4-{[(CH₃)₂NC(S)]₂N-}benzyl,
N-Boc-2-aminoethyl-, 4-[(1,1-dioxothiomorpholin-4-yl)-
 10 C(O)O-]benzyl, 4-[(CH₃)₂NS(O)₂-]benzyl, 4-(imidazolid-2'-one-1'-yl)benzyl,
 4-[(piperidin-1'-yl)C(O)O-]benzyl, 1-N-benzyl-imidazol-4-yl-CH₂-, 3,4-
 dioxyethylenebenzyl, 3,4-dioxymethylenebenzyl,
 4-[N(SO₂)(CH₃)CH₂CH₂CH₂N(CH₃)₂]benzyl, 4-(3'-formylimidazolid-2'-
 one-1'-yl)benzyl, 4-[NHC(O)CH(CH₂CH₂CH₂CH₂NH₂)NHBoc]-benzyl,
 15 [2'-[4"-hydroxy-4''-(3'''-methoxythien-2'''-yl)piperidin-2"-yl]ethoxy]benzyl,
 and *p*-[(CH₃)₂NCH₂CH₂N(CH₃)C(O)O-]benzyl.

In the compounds of formula IA, R⁶ is preferably 2,4-dioxo-
 tetrahydrofuran-3-yl (3,4-enol), methoxy, ethoxy, *iso*-propoxy, *n*-butoxy,
 20 *t*-butoxy, cyclopentoxy, *neo*-pentoxy, 2- α -*iso*-propyl-4- β -
 methylcyclohexoxy, 2- β -isopropyl-4- β -methylcyclohexoxy,
 -NH₂, benzyloxy, -NHCH₂COOH, -NHCH₂CH₂COOH, -NH-adamantyl,
 -NHCH₂CH₂COOCH₂CH₃, -NHSO₂-*p*-CH₃- ϕ , -NHOR⁸ where R⁸ is
 hydrogen, methyl, *iso*-propyl or benzyl, O-(N-succinimidyl),
 25 -O-cholest-5-en-3- β -yl, -OCH₂-OC(O)C(CH₃)₃, -O(CH₂)_zNHC(O)W where *z*
 is 1 or 2 and W is selected from the group consisting of pyrid-3-yl, N-
 methylpyridyl, and N-methyl-1,4-dihydro-pyrid-3-yl, -NR''C(O)-R' where
 R' is aryl, heteroaryl or heterocyclic and R'' is hydrogen or
 -CH₂C(O)OCH₂CH₃.

N-(toluene-4-sulfonyl)cycloleucyl-L-phenylalanine;

***N*-(2-methoxycarbonylbenzenesulfonyl)- α -methylalanyl-L-phenylalanine;**

***N*-(toluene-4-sulfonyl)-L- α -methylprolyl-L-phenylalanine;**

***N*-(toluene-4-sulfonyl)-*N*-methyl- α -methylalanyl-L-(4-nitro)phenylalanine ethyl ester;**

N-(toluene-4-sulfonyl)-*N*-methyl- α -methylalanyl-L-phenylalanine;

N-(toluene-4-sulfonyl)-*N*-methyl- α -methylalanyl-L-4-(*N*-*tert*-butyloxycarbonylisonipecotamido)phenylalanine methyl ester;

***N*-(toluene-4-sulfonyl)-*N*-methylcycloleucyl-L-phenylalanine;**

***N*-(benzenesulfonyl)-*N*-methyl- α -methylalanyl-L-phenylalanine ethyl ester;**

***N*-(toluene-4-sulfonyl)-*N*-methyl- α -methylalanyl-L-4-(isonipecotamido)phenylalanine methyl ester;**

***N*-(benzenesulfonyl)-*N*-methyl- α -methylalanyl-L-phenylalanine;**

[1-(*N*-(toluene-4-sulfonyl)-*N*-methyamino)cyclohexyl-1-carbonyl]-L-phenylalanine;

***N*-(toluene-4-sulfonyl)-*N*-methylcycloleucyl-L-4-(isonicotinamido)phenylalanine ethyl ester;**

***N*-(toluene-4-sulfonyl)-*N*-methylcycloleucyl-L-4-(2-bromobenzamido)phenylalanine;**

N-(toluene-4-sulfonyl)-*N*-methylcycloleucyl-L-4-(*N*-tert-butylloxycarbonylisonipecotamido)phenylalanine methyl ester;

***N*-(toluene-4-sulfonyl)-*N*-methylcycloleucyl-L-4-(isonicotinamido)phenylalanine methyl ester;**

N-(toluene-4-sulfonyl)-*N*-methylcycloleucyl-L-4-(2-*tert*-

butyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamido)phenylalanine methyl ester;

5 *N*-(toluene-4-sulfonyl)-*N*-methylcycloleucyl-L-4-(isonicotinamido)phenylalanine;

N-(toluene-4-sulfonyl)-*N*-methylcycloleucyl-L-4-(2-bromobenzamido)phenylalanine methyl ester;

10 *N*-(toluene-4-sulfonyl)-*N*-methylcycloleucyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine methyl ester;

15 *N*-(toluene-4-sulfonyl)-*N*-methylcycloleucyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine ethyl ester;

N-(toluene-4-sulfonyl)-*N*-methylcycloleucyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine;

20 *N*-(toluene-4-sulfonyl)-*N*-methylcycloleucyl-L-4-(1-methylpiperidin-4-oxy)phenylalanine ethyl ester;

[1-(*N*-(toluene-4-sulfonyl)-*N*-methylamino)cyclobutyl-1-carbonyl]-L-phenylalanine methyl ester;

25 *N*-(toluene-4-sulfonyl)-L- α -methylprolyl-L-4-(isonicotinamido)phenylalanine methyl ester;

[1-(*N*-(toluene-4-sulfonyl)-*N*-methylamino)cyclobutyl-1-carbonyl]-L-phenylalanine;

30 *N*-(toluene-4-sulfonyl)-L- α -methylprolyl-L-4-(isonicotinamido)phenylalanine;

35 *N*-(toluene-4-sulfonyl)-*N*-methylcycloleucyl-L-4-(1-methylpiperidin-4-oxy)phenylalanine methyl ester;

[1-(*N*-(toluene-4-sulfonyl)-*N*-methylamino)cyclopropyl-1-carbonyl]-L-phenylalanine;

40 *N*-(toluene-4-sulfonyl)-*N*-methylcycloleucyl-L-4-(isonipecotamido)phenylalanine;

[1-(*N*-(toluene-4-sulfonyl)-*N*-methylamino)cyclopropyl-1-carbonyl]-L-phenylalanine methyl ester;

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- N*-(toluene-4-sulfonyl)-*N*-methylcycloleucyl-L-4-(1-methylpiperidin-4-oxy)phenylalanine;
- 5 *N*-(toluene-4-sulfonyl)- α -methylprolyl-L-4-(1-methylpiperidin-4-oxy)phenylalanine ethyl ester;
- 10 *N*-(α -toluenesulfonyl)-*N*-methylcycloleucyl-L-4-(1-methylpiperidin-4-oxy)phenylalanine methyl ester;
- 15 *N*-(toluene-4-sulfonyl)- α -methylprolyl-L-4-(1-methylpiperidin-4-oxy)phenylalanine;
- 20 *N*-(α -toluenesulfonyl)-*N*-methylcycloleucyl-L-4-(isonicotinamido)phenylalanine ethyl ester;
- 25 *N*-(α -toluenesulfonyl)cycloleucyl-L-phenylalanine;
- 30 *N*-(α -toluenesulfonyl)-*N*-methylcycloleucyl-L-4-(2-bromobenzamido)phenylalanine ethyl ester;
- 35 *N*-(α -toluenesulfonyl)-*N*-methylcycloleucyl-L-4-(1-methylpiperidin-4-oxy)phenylalanine;
- 40 *N*-(α -toluenesulfonyl)-*N*-methylcycloleucyl-L-4-(isonicotinamido)phenylalanine;
- 45 *N*-(α -toluenesulfonyl)-*N*-methylcycloleucyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester;
- 50 *N*-(toluene-4-sulfonyl)-*N*-methylcycloleucyl-D-phenylalanine methyl ester;
- 55 *N*-(α -toluenesulfonyl)-*N*-methylcycloleucyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine;
- 60 *N*-(toluene-4-sulfonyl)- α -methylprolyl-L-4-(4-methylpiperazin-1-carbonyloxy)phenylalanine *tert*-butyl ester;
- 65 *N*-(toluene-4-sulfonyl)- α -methylprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester;
- 70 *N*-(toluene-4-sulfonyl)- α -methylprolyl-L-4-(4-methylpiperazin-1-

0123456789101112131415161718192021222324252627282930313233343536373839404142434445464748495051525354555657585960616263646566676869707172737475767778798081828384858687888990919293949596979899100

carbonyloxy)phenylalanine;

N-(toluene-4-sulfonyl)- α -methylprolyl-L-tyrosine *tert*-butyl ester;

5 *N*-(α -toluenesulfonyl)-*N*-methyl- α -methylalanyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine;

N-(toluene-4-sulfonyl)-*N*-methylcycloleucyl-D-4-(*N,N*-dimethylcarbamyloxy)phenylalanine;

10 *N*-(toluene-4-sulfonyl)- α -methylprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine;

15 *N*-(toluene-4-sulfonyl)- α -methylprolyl-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine *tert*-butyl ester;

N-(toluene-4-sulfonyl)- α -methylprolyl-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine;

20 *N*-(toluene-4-sulfonyl)- α -methylprolyl-D-tyrosine *tert*-butyl ester;

N-(toluene-4-sulfonyl)-*N*-methylcycloleucyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester;

25 *N*-(toluene-4-sulfonyl)- α -methylprolyl-L-4-(morpholin-4-ylcarbonyloxy)phenylalanine 1-(trimethyacetoxymethyl ester);

30 *N*-(toluene-4-sulfonyl)- α -methylprolyl-L-4-[*N*-(2-(*N'*,*N'*-dimethylamino)ethyl)-*N*-methylcarbamyloxy]phenylalanine *tert*-butyl ester;

N-(toluene-4-sulfonyl)- α -methylprolyl-L-4-[*N*-(2-(*N'*,*N'*-dimethylamino)ethyl)-*N*-methylcarbamyloxy]phenylalanine;

35 *N*-(4-fluorobenzenesulfonyl)- α -methylprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-butyl ester;

N-(4-fluorobenzenesulfonyl)- α -methylprolyl-L-4-(*N,N*-dimethylcarbamyloxy)phenylalanine

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and pharmaceutically acceptable salts thereof as well as any of the ester compounds recited above wherein one ester is replaced with another

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ester selected from the group consisting of methyl ester, ethyl ester, *n*-propyl ester, isopropyl ester, *n*-butyl ester, isobutyl ester, *sec*-butyl ester and *tert*-butyl ester.

5 This invention also provides methods for binding VLA-4 in a biological sample which method comprises contacting the biological sample with a compound of formula I or IA above under conditions wherein said compound binds to VLA-4.

10 Certain of the compounds of formula I and IA above are also useful in reducing VLA-4 mediated inflammation *in vivo*.

15 This invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of one or more of the compounds of formula I or IA above with the exception that R³ and R⁵ are derived from L-amino acids or other similarly configured starting materials. Alternatively, racemic mixtures can be used.

20 The pharmaceutical compositions may be used to treat VLA-4 mediated disease conditions. Such disease conditions include, by way of example, asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes (including acute juvenile onset diabetes), inflammatory bowel disease (including ulcerative colitis and Crohn's disease), multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis, meningitis, 25 encephalitis, stroke, and other cerebral traumas, nephritis, retinitis, atopic dermatitis, psoriasis, myocardial ischemia and acute leukocyte-mediated lung injury such as that which occurs in adult respiratory distress syndrome.

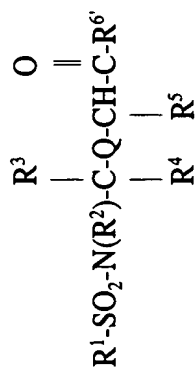
30 Accordingly, this invention also provides methods for the treatment of an inflammatory disease in a patient mediated by VLA-4 which methods

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comprise administering to the patient the pharmaceutical compositions described above.

Preferred compounds of formula I and IA above include those set
5 forth in Table I below:

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R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = -C(O)NR ⁷
<i>p</i> -CH ₃ - φ-	H	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - cyclopentyl		-CH ₂ -φ	-OH	H
<i>o</i> - methox y- carbony l-φ-	H	-CH ₃	-CH ₃	-CH ₂ -φ	-OH	H
<i>p</i> -CH ₃ - φ-	R ² /R ³ = cyclic 3 carbon atoms (L- pyrrolidi nyl)		-CH ₃	-CH ₂ -φ	-OH	H
<i>p</i> -CH ₃ - φ-	-CH ₃	-CH ₃	-CH ₃	<i>p</i> -(nitro)benzyl-	-OCH ₂ CH ₃	H

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R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = -C(O)NR ⁷ - R ⁷
<i>p</i> -CH ₃ - φ-	-CH ₃	-CH ₃	-CH ₃	-CH ₂ -φ	-OH	H
<i>p</i> -CH ₃ - φ-	-CH ₃	-CH ₃	-CH ₃	<i>p</i> -[(1-Boc-piperidin-4-yl)C(O)NH-]benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ - φ-	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		-CH ₂ -φ	-OH	H
φCH ₂ -	-CH ₃	-CH ₃	-CH ₃	-CH ₂ -φ	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ - φ-	-CH ₃	-CH ₃	-CH ₃	<i>p</i> -[(piperidin-4-yl)C(O)NH-]benzyl-	-OCH ₃	H
φCH ₂ -	-CH ₃	-CH ₃	-CH ₃	-CH ₂ -φ	-OH	H
<i>p</i> -CH ₃ - φ-	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ - CH ₂ CH ₂ - (cyclohexyl)		-CH ₂ -φ	-OH	H
<i>p</i> -CH ₃ - φ-	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(2-bromophenyl)C(O)NH-]benzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ - φ-	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(pyridin-4-yl)C(O)NH-]benzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ - φ-	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(2-bromophenyl)C(O)NH-]benzyl-	-OH	H

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R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = -C(O)NR ⁷ - R ⁷
<i>p</i> -CH ₃ - φ	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(1-Boc-piperidin-4-yl)C(O)NH-]benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ - φ	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(pyridin-4-yl)C(O)NH-]benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ - φ	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(2-Boc-1,2,3,4-tetrahydroquinolin-1-yl)C(O)NH-]benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ - φ	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(pyridin-4-yl)C(O)NH-]benzyl-	-OH	H
<i>p</i> -CH ₃ - φ	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(2-bromophenyl)C(O)NH-]benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ - φ	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(4-(CH ₃) ₂ NC(O)O-)benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ - φ	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(4-(CH ₃) ₂ NC(O)O-)benzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ - φ	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(4-(CH ₃) ₂ NC(O)O-)benzyl-	-OH	H
<i>p</i> -CH ₃ - φ	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(1-methylpiperidin-4-yl)-O-]benzyl-	-OCH ₂ CH ₃	H

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R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = -C(O)NR ⁷ - R ⁷
<i>p</i> -CH ₃ - φ-	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ - (cyclobutyl)		-CH ₂ -φ	-OCH ₃	H
<i>p</i> -CH ₃ - φ-	R ² /R ³ = cyclic 3 carbon atoms (L- pyrrolidi nyl)		-CH ₃	<i>p</i> -(pyridin-4-yl)-C(O)NHbenzyl-	-OCH ₃	H
<i>p</i> -CH ₃ - φ-	CH ₃ -	R ³ /R ⁴ = cyclic 3 carbon atoms (cyclobutyl)		-CH ₂ -φ	-OH	H
<i>p</i> -CH ₃ - φ-	R ² /R ³ = cyclic 3 carbon atoms (L- pyrrolidi nyl)		-CH ₃	<i>p</i> -(pyridin-4-yl)-C(O)NHbenzyl-	-OH	H
<i>p</i> -CH ₃ - φ-	CH ₃ -	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(1-methylpiperidin-4-yl)-O-]benzyl-	-OCH ₃	H
<i>p</i> -CH ₃ - φ-	CH ₃ -	R ³ /R ⁴ = -CH ₂ CH ₂ - (cyclopropyl)		-CH ₂ -φ	-OH	H
<i>p</i> -CH ₃ - φ-	CH ₃ -	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(piperidin-4-yl)C(O)NH-]benzyl-	-OH	H

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = -C(O)NR ⁷ - R ⁷
<i>p</i> -CH ₃ - φ-	CH ₃ -	R ³ /R ⁴ = -CH ₂ CH ₂ - (cyclopropyl)		-CH ₂ -φ	-OCH ₃	H
<i>p</i> -CH ₃ - φ-	CH ₃ -	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(1-methylpiperidin-4-yl)-O-]benzyl-	-OH	H
<i>p</i> -CH ₃ - φ-	R ² /R ³ = cyclic 3 carbon atoms (L- pyrrolidi nyl)		-CH ₃	<i>p</i> -[(1-methylpiperidin-4-yl)-O-]benzyl-	-OCH ₂ CH ₃	H
φ-CH ₂ -	CH ₃ -	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(1-methylpiperidin-4-yl)-O-]benzyl-	-OCH ₃	H
φ-CH ₂ -	CH ₃ -	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(1-methylpiperidin-4-yl)-O-]benzyl-	-OCH ₂ CH ₃	H
<i>p</i> -CH ₃ - φ-	R ² /R ³ = cyclic 3 carbon atoms (L- pyrrolidi nyl)		-CH ₃	<i>p</i> -[(1-methylpiperidin-4-yl)-O-]benzyl-	-OH	H
φ-CH ₂ -	CH ₃ -	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -(pyridin-4-yl-C(O)NH)benzyl-	-OCH ₂ CH ₃	H

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = -C(O)NR ⁷ - R ⁷
φ-CH ₂ -	H	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		-CH ₂ -φ	-OH	H
φ-CH ₂ -	CH ₃ -	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(2-bromophenyl)C(O)NH-]benzyl-	-OCH ₂ CH ₃	H
φ-CH ₂ -	CH ₃ -	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(2-bromophenyl)C(O)NH-]benzyl-	-OCH ₂ CH ₃	H
φ-CH ₂ -	CH ₃ -	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(1-methylpiperidin-4-yl)-O-]benzyl-	-OH	H
φ-CH ₂ -	CH ₃ -	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -(pyridin-4-yl)-C(O)NHbenzyl-	-OH	H
φ-CH ₂ -	CH ₃ -	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(CH ₃) ₂ NC(O)O-]benzyl-	-OC(CH ₃) ₃	H
<i>p</i> -CH ₃ - φ-	CH ₃ -	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		-CH ₂ -φ	-OCH ₃	H
φ-CH ₂ -	CH ₃ -	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(CH ₃) ₂ NC(O)O-]benzyl-	-OH	H

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = -C(O)NR ⁷ -
<i>p</i> -CH ₃ - φ-	R ² /R ³ = cyclic 3 carbon atoms (L- pyrrolidi nyl)		-CH ₃	<i>p</i> -[(4-methylpiperazin-1-yl)C(O)O-]benzyl-	-OC(CH ₃) ₃	H
<i>p</i> -CH ₃ - φ-	R ² /R ³ = cyclic 3 carbon atoms (L- pyrrolidi nyl)		-CH ₃	<i>p</i> -[(CH ₃) ₂ NC(O)O-]benzyl-	-OC(CH ₃) ₃	H
<i>p</i> -CH ₃ - φ-	R ² /R ³ = cyclic 3 carbon atoms (L- pyrrolidi nyl)		-CH ₃	<i>p</i> -[(4-methylpiperazin-1-yl)C(O)O-]benzyl-	-OH	H
φ-CH ₂ -	CH ₃ -	CH ₃ -	CH ₃ -	<i>p</i> -[(CH ₃) ₂ NC(O)O-]benzyl-	-OH	H
<i>p</i> -CH ₃ - φ-	CH ₃ -	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(CH ₃) ₂ NC(O)O-]benzyl-	-OH	H

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = -C(O)NR ⁷
<i>p</i> -CH ₃ - φ	R ² /R ³ = cyclic 3 carbon atoms (L- pyrrolidi nyl)		-CH ₃	<i>p</i> -[(CH ₃) ₂ NC(O)O-]benzyl-	-OH	H
<i>p</i> -CH ₃ - φ	R ² /R ³ = cyclic 3 carbon atoms (L- pyrrolidi nyl)		-CH ₃	<i>p</i> -[(morpholin-4-yl)C(O)O-]benzyl-	-OC(CH ₃) ₃	H
<i>p</i> -CH ₃ - φ	R ² /R ³ = cyclic 3 carbon atoms (L- pyrrolidi nyl)		-CH ₃	<i>p</i> -[(morpholin-4-yl)C(O)O-]benzyl-	-OH	H
<i>p</i> -CH ₃ - φ	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(CH ₃) ₂ NC(O)O-]benzyl-	-OC(CH ₃) ₃	H

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = -C(O)NR ⁷ - R ⁷
<i>p</i> -CH ₃ - φ	R ² /R ³ = cyclic 3 carbon atoms (L- pyrrolidi nyl)		-CH ₃	<i>p</i> -[(morpholin-4-yl)C(O)O-]benzyl-	-OCH ₂ O- C(O)- C(CH ₃) ₃	H
<i>p</i> -CH ₃ - φ	R ² /R ³ = cyclic 3 carbon atoms (L- pyrrolidi nyl)		-CH ₃	<i>p</i> -[(CH ₃) ₂ NCH ₂ CH ₂ N(CH ₃)C(O)O-]benzyl	-OC(CH ₃) ₃	H
<i>p</i> -CH ₃ - φ	R ² /R ³ = cyclic 3 carbon atoms (L- pyrrolidi nyl)		-CH ₃	<i>p</i> -[(CH ₃) ₂ NCH ₂ CH ₂ N(CH ₃)C(O)O-]benzyl	-OH	H
<i>p</i> -F-φ	R ² /R ³ = cyclic 3 carbon atoms (L- pyrrolidi nyl)		-CH ₃	<i>p</i> -[(CH ₃) ₂ NC(O)O-]benzyl	-OC(CH ₃) ₃	H

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = -C(O)NR ⁷ -
<i>p</i> -F-φ	R ² /R ³ = cyclic 3 carbon atoms (L- pyrrolidi nyl)		-CH ₃	<i>p</i> -[(CH ₃) ₂ NC(O)O-]benzyl	-OH	H

DETAILED DESCRIPTION OF THE INVENTION

As above, this invention relates to compounds which inhibit leukocyte adhesion and, in particular, leukocyte adhesion mediated by VLA-4. However, prior to describing this invention in further detail, the following terms will first be defined.

Definitions

As used herein, "alkyl" refers to alkyl groups preferably having from 1 to 10 carbon atoms and more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methyl, t-butyl, n-heptyl, octyl and the like.

"Substituted alkyl" refers to an alkyl group, preferably of from 1 to 10 carbon atoms, having from 1 to 5 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxylaryl, substituted aryloxyaryl, cyano, halogen, hydroxyl, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted aryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-\text{OS}(\text{O})_2\text{-alkyl}$, $-\text{OS}(\text{O})_2\text{-substituted alkyl}$, $-\text{OS}(\text{O})_2\text{-aryl}$, $-\text{OS}(\text{O})_2\text{-substituted aryl}$, $-\text{OS}(\text{O})_2\text{-}$

heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR where R is hydrogen or alkyl, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and substituted alkyl groups having amino groups blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or alkyl/substituted alkyl groups substituted with -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl, -SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-substituted heterocyclic and -SO₂NRR where R is hydrogen or alkyl.

"Alkoxy" refers to the group "alkyl-O-" which includes, by way of example, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like.

"Substituted alkoxy" refers to the group "substituted alkyl-O-".

"Acyl" refers to the groups H-C(O)-, alkyl-C(O)-, substituted alkyl-C(O)-, alkenyl-C(O)-, substituted alkenyl-C(O)-, alkynyl-C(O)-, substituted

alkynyl-C(O)- cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, aryl-C(O)-, substituted aryl-C(O)-, heteroaryl-C(O)-, substituted heteroaryl-C(O), heterocyclic-C(O)-, and substituted heterocyclic-C(O)- wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Acylamino" refers to the group -C(O)NRR where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and where each R is joined to form together with the nitrogen atom a heterocyclic or substituted heterocyclic ring wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Thiocarbonylamino" refers to the group -C(S)NRR where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and where each R is joined to form, together with the nitrogen atom a heterocyclic or substituted heterocyclic ring wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Acyloxy" refers to the groups alkyl-C(O)O-, substituted alkyl-C(O)O-, alkenyl-C(O)O-, substituted alkenyl-C(O)O-, alkynyl-C(O)O-, substituted alkynyl-C(O)O-, aryl-C(O)O-, substituted aryl-C(O)O-, cycloalkyl-C(O)O-, substituted cycloalkyl-C(O)O-, heteroaryl-C(O)O-, substituted heteroaryl-C(O)O-, heterocyclic-C(O)O-, and substituted heterocyclic-C(O)O- wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Alkenyl" refers to alkenyl group preferably having from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-2 sites of alkenyl unsaturation.

"Substituted alkenyl" refers to alkenyl groups having from 1 to 5 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino,

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-OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR where R is hydrogen or alkyl, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and substituted alkenyl groups having amino groups blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or alkenyl/substituted alkenyl groups substituted with -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl, -SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-substituted heterocyclic and -SO₂NRR where R is hydrogen or alkyl.

25 "Alkynyl" refers to alkynyl group preferably having from 2 to 10 carbon atoms and more preferably 3 to 6 carbon atoms and having at least 1 and preferably from 1-2 sites of alkynyl unsaturation.

30 "Substituted alkynyl" refers to alkynyl groups having from 1 to 5 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino,

alkylamidino, thioamidino, aminoacyl, aminocarbonylamino,
aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy,
substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl,
cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-
5 cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-
substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl,
carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl,
substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl,
substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl,
10 substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl,
thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted
heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted
cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy,
substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino,
15 -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted
aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-
heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR where R is
hydrogen or alkyl, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-
aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted
20 heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic,
-NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl,
-NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-
substituted heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted
heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono-
25 and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-
substituted arylamino, mono- and di-heteroarylamino, mono- and di-
substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and
di-substituted heterocyclic amino, unsymmetric di-substituted amines having
different substituents selected from alkyl, substituted alkyl, aryl, substituted
30 aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted
heterocyclic and substituted alkynyl groups having amino groups blocked by

conventional blocking groups such as Boc, Cbz, formyl, and the like or alkynyl/substituted alkynyl groups substituted with -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl, -SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-substituted heterocyclic and -SO₂NRR where R is hydrogen or alkyl.

"Amidino" refers to the group H₂NC(=NH)- and the term "alkylamidino" refers to compounds having 1 to 3 alkyl groups (e.g., alkylHNC(=NH)-).

"Thioamidino" refers to the group RSC(=NH)- where R is hydrogen or alkyl.

"Aminoacyl" refers to the groups -NRC(O)alkyl, -NRC(O)substituted alkyl, -NRC(O)cycloalkyl, -NRC(O)substituted cycloalkyl, -NRC(O)alkenyl, -NRC(O)substituted alkenyl, -NRC(O)alkynyl, -NRC(O)substituted alkynyl, -NRC(O)aryl, -NRC(O)substituted aryl, -NRC(O)heteroaryl, -NRC(O)substituted heteroaryl, -NRC(O)heterocyclic, and -NRC(O)substituted heterocyclic where R is hydrogen or alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminocarbonyloxy" refers to the groups -NRC(O)O-alkyl, -NRC(O)O-substituted alkyl, -NRC(O)O-alkenyl, -NRC(O)O-substituted alkenyl, -NRC(O)O-alkynyl, -NRC(O)O-substituted alkynyl, -NRC(O)O-cycloalkyl, -NRC(O)O-substituted cycloalkyl, -NRC(O)O-aryl, -NRC(O)O-substituted aryl, -NRC(O)O-heteroaryl, -NRC(O)O-substituted heteroaryl,

-NRC(O)O-heterocyclic, and -NRC(O)O-substituted heterocyclic where R is hydrogen or alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Oxycarbonylamino" refers to the groups -OC(O)NH₂, -OC(O)NRR, -OC(O)NR-alkyl, -OC(O)NR-substituted alkyl, -OC(O)NR-alkenyl, -OC(O)NR-substituted alkenyl, -OC(O)NR-alkynyl, -OC(O)NR-substituted alkynyl, -OC(O)NR-cycloalkyl, -OC(O)NR-substituted cycloalkyl, -OC(O)NR-aryl, -OC(O)NR-substituted aryl, -OC(O)NR-heteroaryl, -OC(O)NR-substituted heteroaryl, -OC(O)NR-heterocyclic, and -OC(O)NR-substituted heterocyclic where R is hydrogen, alkyl or where each R is joined to form, together with the nitrogen atom a heterocyclic or substituted heterocyclic ring and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Oxythiocarbonylamino" refers to the groups -OC(S)NH₂, -OC(S)NRR, -OC(S)NR-alkyl, -OC(S)NR-substituted alkyl, -OC(S)NR-alkenyl, -OC(S)NR-substituted alkenyl, -OC(S)NR-alkynyl, -OC(S)NR-substituted alkynyl, -OC(S)NR-cycloalkyl, -OC(S)NR-substituted cycloalkyl, -OC(S)NR-aryl, -OC(S)NR-substituted aryl, -OC(S)NR-heteroaryl, -OC(S)NR-substituted heteroaryl, -OC(S)NR-heterocyclic, and -OC(S)NR-substituted heterocyclic where R is hydrogen, alkyl or where each R is joined to form together with the nitrogen atom a heterocyclic or substituted heterocyclic ring and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminocarbonylamino" refers to the groups -NRC(O)NRR,
-NRC(O)NR-alkyl, -NRC(O)NR-substituted alkyl, -NRC(O)NR-alkenyl,
-NRC(O)NR-substituted alkenyl, -NRC(O)NR-alkynyl,
-NRC(O)NR-substituted alkynyl, -NRC(O)NR-aryl, -NRC(O)NR-substituted
5 aryl, -NRC(O)NR-cycloalkyl, -NRC(O)NR-substituted cycloalkyl, -
NRC(O)NR-heteroaryl, and -NRC(O)NR-substituted heteroaryl, -
NRC(O)NR-heterocyclic, and -NRC(O)NR-substituted heterocyclic where
each R is independently hydrogen, alkyl or where each R is joined to form
together with the nitrogen atom a heterocyclic or substituted heterocyclic
10 ring as well as where one of the amino groups is blocked by conventional
blocking groups such as Boc, Cbz, formyl, and the like and wherein alkyl,
substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl,
cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl,
substituted heteroaryl, heterocyclic and substituted heterocyclic are as
15 defined herein.

"Aminothiocabonylamino" refers to the groups -NRC(S)NRR,
-NRC(S)NR-alkyl, -NRC(S)NR-substituted alkyl, -NRC(S)NR-alkenyl,
-NRC(S)NR-substituted alkenyl, -NRC(S)NR-alkynyl, -NRC(S)NR-
20 substituted alkynyl, -NRC(S)NR-aryl, -NRC(S)NR-substituted aryl,
-NRC(S)NR-cycloalkyl, -NRC(S)NR-substituted cycloalkyl, -NRC(S)NR-
heteroaryl, and -NRC(S)NR-substituted heteroaryl, -NRC(S)NR-
heterocyclic, and -NRC(S)NR-substituted heterocyclic where each R is
independently hydrogen, alkyl or where each R is joined to form together
25 with the nitrogen atom a heterocyclic or substituted heterocyclic ring as well
as where one of the amino groups is blocked by conventional blocking
groups such as Boc, Cbz, formyl, and the like and wherein alkyl, substituted
alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl,
substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted
30 heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aryl" or "Ar" refers to an unsaturated aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (e.g., phenyl) or multiple condensed rings (e.g., naphthyl or anthryl) which condensed rings may or may not be aromatic (e.g., 2-benzoxazolinone, 2H-1,4-benzoxazin-3(4H)-one-7yl, and the like). Preferred aryls include phenyl and naphthyl.

Substituted aryl refers to aryl groups which are substituted with from 1 to 3 substituents selected from the group consisting of hydroxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amidino, alkylamidino, thioamidino, amino, aminoacyl, aminocarbonyloxy, aminocarbonylamino, aminothiocarbonylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, carboxylamido, cyano, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thioheteroaryl, substituted thioheteroaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheterocyclic, substituted thioheterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, halo, nitro, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -S(O)₂-alkyl, -S(O)₂-substituted alkyl, -S(O)₂-cycloalkyl, -S(O)₂-substituted cycloalkyl, -S(O)₂-alkenyl, -S(O)₂-substituted alkenyl, -S(O)₂-aryl, -S(O)₂-substituted aryl, -S(O)₂-heteroaryl, -S(O)₂-substituted heteroaryl, -S(O)₂-heterocyclic, -S(O)₂-substituted heterocyclic, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl,

-OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR where R is hydrogen or alkyl, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and amino groups on the substituted aryl blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or substituted with -SO₂NRR where R is hydrogen or alkyl.

"Aryloxy" refers to the group aryl-O- which includes, by way of example, phenoxy, naphthoxy, and the like.

"Substituted aryloxy" refers to substituted aryl-O- groups.

"Aryloxyaryl" refers to the group -aryl-O-aryl.

"Substituted aryloxyaryl" refers to aryloxyaryl groups substituted with from 1 to 3 substituents on either or both aryl rings selected from the group consisting of hydroxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted

- alkenyl, alkynyl, substituted alkynyl, amidino, alkylamidino, thioamidino, amino, aminoacyl, aminocarbonyloxy, aminocarbonylamino, aminothiocabonylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted
- 5 heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, carboxylamido, cyano, thiol, thioalkyl,
- 10 substituted thioalkyl, thioaryl, substituted thioaryl, thioheteroaryl, substituted thioheteroaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheterocyclic, substituted thioheterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, halo, nitro, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted
- 15 cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -S(O)₂-alkyl, -S(O)₂-substituted alkyl, -S(O)₂-cycloalkyl, -S(O)₂-substituted cycloalkyl, -S(O)₂-alkenyl, -S(O)₂-substituted alkenyl, -S(O)₂-aryl, -S(O)₂-substituted aryl, -S(O)₂-heteroaryl, -S(O)₂-substituted heteroaryl, -S(O)₂-
- 20 heterocyclic, -S(O)₂-substituted heterocyclic, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR where R is hydrogen or alkyl, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl, -NRS(O)₂-
- 25 substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted
- 30 heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-

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substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and amino groups on the substituted aryl blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or substituted with -SO₂NRR where R is hydrogen or alkyl.

10 "Cycloalkyl" refers to cyclic alkyl groups of from 3 to 8 carbon atoms having a single cyclic ring including, by way of example, cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl and the like. Excluded from this definition are multi-ring alkyl groups such as adamantanyl, etc.

15 "Cycloalkenyl" refers to cyclic alkenyl groups of from 3 to 8 carbon atoms having single or multiple unsaturation but which are not aromatic.

"Substituted cycloalkyl" and "substituted cycloalkenyl" refer to a cycloalkyl and cycloalkenyl groups, preferably of from 3 to 8 carbon atoms, having from 1 to 5 substituents selected from the group consisting of oxo (=O), thioxo (=S), alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl,

thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted
thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted
heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy,
substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy,
5 oxycarbonylamino, oxythiocarbonylamino, $-\text{OS}(\text{O})_2\text{-alkyl}$, $-\text{OS}(\text{O})_2\text{-}$
substituted alkyl, $-\text{OS}(\text{O})_2\text{-aryl}$, $-\text{OS}(\text{O})_2\text{-substituted aryl}$, $-\text{OS}(\text{O})_2\text{-heteroaryl}$,
 $-\text{OS}(\text{O})_2\text{-substituted heteroaryl}$, $-\text{OS}(\text{O})_2\text{-heterocyclic}$, $-\text{OS}(\text{O})_2\text{-substituted}$
heterocyclic, $-\text{OSO}_2\text{-NRR}$ where R is hydrogen or alkyl,
 $-\text{NRS}(\text{O})_2\text{-alkyl}$, $-\text{NRS}(\text{O})_2\text{-substituted alkyl}$, $-\text{NRS}(\text{O})_2\text{-aryl}$, $-\text{NRS}(\text{O})_2\text{-}$
10 substituted aryl, $-\text{NRS}(\text{O})_2\text{-heteroaryl}$, $-\text{NRS}(\text{O})_2\text{-substituted heteroaryl}$,
 $-\text{NRS}(\text{O})_2\text{-heterocyclic}$, $-\text{NRS}(\text{O})_2\text{-substituted heterocyclic}$,
 $-\text{NRS}(\text{O})_2\text{-NR-alkyl}$, $-\text{NRS}(\text{O})_2\text{-NR-substituted alkyl}$, $-\text{NRS}(\text{O})_2\text{-NR-aryl}$,
 $-\text{NRS}(\text{O})_2\text{-NR-substituted aryl}$, $-\text{NRS}(\text{O})_2\text{-NR-heteroaryl}$, $-\text{NRS}(\text{O})_2\text{-NR-}$
substituted heteroaryl, $-\text{NRS}(\text{O})_2\text{-NR-heterocyclic}$, $-\text{NRS}(\text{O})_2\text{-NR-substituted}$
15 heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono-
and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-
substituted arylamino, mono- and di-heteroarylamino, mono- and di-
substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and
di-substituted heterocyclic amino, unsymmetric di-substituted amines having
20 different substituents selected from alkyl, substituted alkyl, aryl, substituted
aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted
heterocyclic and substituted alkynyl groups having amino groups blocked by
conventional blocking groups such as Boc, Cbz, formyl, and the like or
alkynyl/substituted alkynyl groups substituted with $-\text{SO}_2\text{-alkyl}$, $-\text{SO}_2\text{-}$
25 substituted alkyl, $-\text{SO}_2\text{-alkenyl}$, $-\text{SO}_2\text{-substituted alkenyl}$, $-\text{SO}_2\text{-cycloalkyl}$,
 $-\text{SO}_2\text{-substituted cycloalkyl}$, $-\text{SO}_2\text{-aryl}$, $-\text{SO}_2\text{-substituted aryl}$, $-\text{SO}_2\text{-}$
heteroaryl, $-\text{SO}_2\text{-substituted heteroaryl}$, $-\text{SO}_2\text{-heterocyclic}$, $-\text{SO}_2\text{-substituted}$
heterocyclic and $-\text{SO}_2\text{NRR}$ where R is hydrogen or alkyl.

30 "Cycloalkoxy" refers to -O-cycloalkyl groups.

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"Substituted cycloalkoxy" refers to -O-substituted cycloalkyl groups.

"Guanidino" refers to the groups -NRC(=NR)NRR,

-NRC(=NR)NR-alkyl, -NRC(=NR)NR-substituted alkyl, -NRC(=NR)NR-alkenyl, -NRC(=NR)NR-substituted alkenyl, -NRC(=NR)NR-alkynyl,
5 -NRC(=NR)NR-substituted alkynyl, -NRC(=NR)NR-aryl,
-NRC(=NR)NR-substituted aryl, -NRC(=NR)NR-cycloalkyl,
-NRC(=NR)NR-heteroaryl, -NRC(=NR)NR-substituted heteroaryl,
-NRC(=NR)NR-heterocyclic, and -NRC(=NR)NR-substituted heterocyclic
where each R is independently hydrogen and alkyl as well as where one of
10 the amino groups is blocked by conventional blocking groups such as Boc,
Cbz, formyl, and the like and wherein alkyl, substituted alkyl, alkenyl,
substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted
cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl,
heterocyclic and substituted heterocyclic are as defined herein.

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"Guanidinosulfone" refers to the groups -NRC(=NR)NRSO₂-alkyl,
-NRC(=NR)NRSO₂-substituted alkyl, -NRC(=NR)NRSO₂-alkenyl,
-NRC(=NR)NRSO₂-substituted alkenyl, -NRC(=NR)NRSO₂-alkynyl,
-NRC(=NR)NRSO₂-substituted alkynyl, -NRC(=NR)NRSO₂-aryl,
20 -NRC(=NR)NRSO₂-substituted aryl, -NRC(=NR)NRSO₂-cycloalkyl,
-NRC(=NR)NRSO₂-substituted cycloalkyl, -NRC(=NR)NRSO₂-heteroaryl,
and -NRC(=NR)NRSO₂-substituted heteroaryl, -NRC(=NR)NRSO₂-
heterocyclic, and -NRC(=NR)NRSO₂-substituted heterocyclic where each R
is independently hydrogen and alkyl and wherein alkyl, substituted alkyl,
25 alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl,
substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted
heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Halo" or "halogen" refers to fluoro, chloro, bromo and iodo and
30 preferably is either chloro or bromo.

"Heteroaryl" refers to an aromatic carbocyclic group of from 2 to 10 carbon atoms and 1 to 4 heteroatoms selected from oxygen, nitrogen and sulfur within the ring. Such heteroaryl groups can have a single ring (e.g., pyridyl or furyl) or multiple condensed rings (e.g., indolizinyl or benzothienyl). Preferred heteroaryls include pyridyl, pyrrolyl, indolyl and furyl.

"Substituted heteroaryl" refers to heteroaryl groups which are substituted with from 1 to 3 substituents selected from the group consisting of hydroxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amidino, alkylamidino, thioamidino, amino, aminoacyl, aminocarbonyloxy, aminocarbonylamino, aminothiocarbonylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, carboxylamido, cyano, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thioheteroaryl, substituted thioheteroaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheterocyclic, substituted thioheterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, halo, nitro, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -S(O)₂-alkyl, -S(O)₂-substituted alkyl, -S(O)₂-cycloalkyl, -S(O)₂-substituted cycloalkyl, -S(O)₂-alkenyl, -S(O)₂-substituted alkenyl, -S(O)₂-aryl, -S(O)₂-substituted aryl, -S(O)₂-heteroaryl, -S(O)₂-substituted heteroaryl, -S(O)₂-heterocyclic, -S(O)₂-substituted heterocyclic, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl,

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-OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR where R is hydrogen or alkyl, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, 5 -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having 15 different substituents selected from alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and amino groups on the substituted aryl blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or substituted with -SO₂NRR where R is hydrogen or alkyl.

20

"Heteroaryloxy" refers to the group -O-heteroaryl and "substituted heteroaryloxy" refers to the group -O-substituted heteroaryl.

25

"Heterocycle" or "heterocyclic" refers to a saturated or unsaturated group having a single ring or multiple condensed rings, from 1 to 10 carbon atoms and from 1 to 4 hetero atoms selected from nitrogen, sulfur or oxygen within the ring wherein, in fused ring systems, one or more of the rings can be aryl or heteroaryl.

30

"Substituted heterocyclic" refers to heterocycle groups which are substituted with from 1 to 3 substituents selected from the group consisting

of oxo (=O), thioxo (=S), alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocabonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)₂-alkyl, -OS(O)₂-substituted alkyl, -OS(O)₂-aryl, -OS(O)₂-substituted aryl, -OS(O)₂-heteroaryl, -OS(O)₂-substituted heteroaryl, -OS(O)₂-heterocyclic, -OS(O)₂-substituted heterocyclic, -OSO₂-NRR where R is hydrogen or alkyl, -NRS(O)₂-alkyl, -NRS(O)₂-substituted alkyl, -NRS(O)₂-aryl, -NRS(O)₂-substituted aryl, -NRS(O)₂-heteroaryl, -NRS(O)₂-substituted heteroaryl, -NRS(O)₂-heterocyclic, -NRS(O)₂-substituted heterocyclic, -NRS(O)₂-NR-alkyl, -NRS(O)₂-NR-substituted alkyl, -NRS(O)₂-NR-aryl, -NRS(O)₂-NR-substituted aryl, -NRS(O)₂-NR-heteroaryl, -NRS(O)₂-NR-substituted heteroaryl, -NRS(O)₂-NR-heterocyclic, -NRS(O)₂-NR-substituted heterocyclic where R is hydrogen or alkyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-substituted arylamino, mono- and di-heteroarylamino, mono- and di-substituted heteroarylamino, mono- and di-heterocyclic amino, mono- and di-substituted heterocyclic amino, unsymmetric di-substituted amines having different substituents selected from alkyl, substituted alkyl, aryl, substituted

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aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and substituted alkynyl groups having amino groups blocked by conventional blocking groups such as Boc, Cbz, formyl, and the like or alkynyl/substituted alkynyl groups substituted with -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-alkenyl, -SO₂-substituted alkenyl, -SO₂-cycloalkyl, -SO₂-substituted cycloalkyl, -SO₂-aryl, -SO₂-substituted aryl, -SO₂-heteroaryl, -SO₂-substituted heteroaryl, -SO₂-heterocyclic, -SO₂-substituted heterocyclic and -SO₂NRR where R is hydrogen or alkyl.

10 Examples of heterocycles and heteroaryls include, but are not limited to, azetidine, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, dihydroindole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, 15 phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, phthalimide, 1,2,3,4-tetrahydroisoquinoline, 4,5,6,7-tetrahydrobenzo[b]thiophene, thiazole, thiazolidine, thiophene, benzo[b]thiophene, morpholino, thiomorpholino, piperidinyl, pyrrolidine, 20 tetrahydrofuranyl, and the like.

"Heterocyclyloxy" refers to the group -O-heterocyclic and "substituted heterocyclyloxy" refers to the group -O-substituted heterocyclic.

25 "Thiol" refers to the group -SH.

"Thioalkyl" refers to the groups -S-alkyl

"Substituted thioalkyl" refers to the group -S-substituted alkyl.

30

"Thiocycloalkyl" refers to the groups -S-cycloalkyl.

"Substituted thiocycloalkyl" refers to the group -S-substituted cycloalkyl.

5 "Thioaryl" refers to the group -S-aryl and "substituted thioaryl" refers to the group -S-substituted aryl.

"Thioheteroaryl" refers to the group -S-heteroaryl and "substituted thioheteroaryl" refers to the group -S-substituted heteroaryl.

10 "Thioheterocyclic" refers to the group -S-heterocyclic and "substituted thioheterocyclic" refers to the group -S-substituted heterocyclic.

15 "Pharmaceutically acceptable salt" refers to pharmaceutically acceptable salts of a compound of Formula I which salts are derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the molecule contains a basic functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate
20 and the like.

Compound Preparation

25 The compounds of this invention can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined
30 by one skilled in the art by routine optimization procedures.

Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups as well as suitable conditions for protecting and deprotecting particular functional groups are well known in the art. For example, numerous protecting groups are described in T. W. Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

Furthermore, the compounds of this invention will typically contain one or more chiral centers. Accordingly, if desired, such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or diastereomers, or as stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) are included within the scope of this invention, unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents and the like.

In a preferred method of synthesis, the compounds of formula I and IA wherein Q is -C(O)NR⁷- are prepared by first coupling an amino acid of formula II:



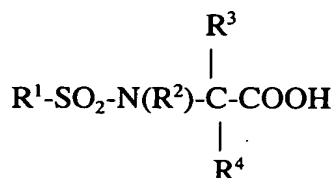
wherein R², R³ and R⁴ are as defined above, with a sulfonyl chloride of formula III:



III

wherein R^1 is as defined above, to provide an *N*-sulfonyl amino acid of formula IV:

5



IV

10

wherein R^1 - R^4 are as defined above.

This reaction is typically conducted by contacting the amino acid of formula II with at least one equivalent, preferably about 1.1 to about 2 equivalents, of sulfonyl chloride III in an inert diluent such as dichloromethane and the like. Generally, the reaction is conducted at a temperature ranging from about $-70^{\circ}C$ to about $40^{\circ}C$ for about 1 to about 24 hours. Preferably, this reaction is conducted in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, tertiary amines, such as triethylamine, diisopropylethylamine, *N*-methylmorpholine and the like. Alternatively, the reaction can be conducted under Schotten-Baumann-type conditions using aqueous alkali, such as sodium hydroxide and the like, as the base. Upon completion of the reaction, the resulting *N*-sulfonyl amino acid IV is recovered by conventional methods including neutralization, extraction, precipitation, chromatography, filtration, and the like.

The amino acids of formula II employed in the above reaction are either known compounds or compounds that can be prepared from known compounds by conventional synthetic procedures. Examples of suitable amino acids for use in this reaction include, but are not limited to, L-proline,

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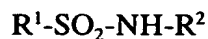
trans-4-hydroxyl-L-proline, *cis*-4-hydroxyl-L-proline, *trans*-3-phenyl-L-proline, *cis*-3-phenyl-L-proline, L-(2-methyl)proline, L-pipecolinic acid, L-azetidine-2-carboxylic acid, L-indoline-2-carboxylic acid, L-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, L-thiazolidine-4-carboxylic acid, L-(5,5-dimethyl)thiazolidine-4-carboxylic acid, L-thiamorpholine-3-carboxylic acid, glycine, 2-*tert*-butylglycine, D,L-phenylglycine, L-alanine, α -methylalanine, *N*-methyl-L-phenylalanine, L-diphenylalanine, sarcosine, D,L-phenylsarcosine, L-aspartic acid β -*tert*-butyl ester, L-glutamic acid γ -*tert*-butyl ester, L-(*O*-benzyl)serine, 1-aminocyclopropanecarboxylic acid, 1-aminocyclobutanecarboxylic acid, 1-aminocyclopentanecarboxylic acid (cycloleucine) 1-aminocyclohexanecarboxylic acid, L-serine and the like. If desired, the corresponding carboxylic acid esters of the amino acids of formula II, such as the methyl esters, ethyl esters and the like, can be employed in the above reaction with the sulfonyl chloride III. Subsequent hydrolysis of the ester group to the carboxylic acid using conventional reagents and conditions, i.e., treatment with an alkali metal hydroxide in an inert diluent such as methanol/water, then provides the *N*-sulfonyl amino acid IV.

20 Similarly, the sulfonyl chlorides of formula III employed in the above reaction are either known compounds or compounds that can be prepared from known compounds by conventional synthetic procedures. Such compounds are typically prepared from the corresponding sulfonic acid, i.e., from compounds of the formula $R^1\text{-SO}_3\text{H}$ where R^1 is as defined above, 25 using phosphorous trichloride and phosphorous pentachloride. This reaction is generally conducted by contacting the sulfonic acid with about 2 to 5 molar equivalents of phosphorous trichloride and phosphorous pentachloride, either neat or in an inert solvent, such as dichloromethane, at temperature in the range of about 0°C to about 80°C for about 1 to about 48 hours to afford 30 the sulfonyl chloride. Alternatively, the sulfonyl chlorides of formula III can be prepared from the corresponding thiol compound, i.e., from compounds

of the formula R^1-SH where R^1 is as defined above, by treating the thiol with chlorine (Cl_2) and water under conventional reaction conditions.

Examples of sulfonyl chlorides suitable for use in this invention include, but are not limited to, methanesulfonyl chloride, 2-propanesulfonyl chloride, 1-butanesulfonyl chloride, benzenesulfonyl chloride, 1-naphthalenesulfonyl chloride, 2-naphthalenesulfonyl chloride, *p*-toluenesulfonyl chloride, α -toluenesulfonyl chloride, 4-acetamidobenzenesulfonyl chloride, 4-amidinobenzenesulfonyl chloride, 4-*tert*-butylbenzenesulfonyl chloride, 4-bromobenzenesulfonyl chloride, 2-carboxybenzenesulfonyl chloride, 4-cyanobenzenesulfonyl chloride, 3,4-dichlorobenzenesulfonyl chloride, 3,5-dichlorobenzenesulfonyl chloride, 3,4-dimethoxybenzenesulfonyl chloride, 3,5-ditrifluoromethylbenzenesulfonyl chloride, 4-fluorobenzenesulfonyl chloride, 4-methoxybenzenesulfonyl chloride, 2-methoxycarbonylbenzenesulfonyl chloride, 4-methylamidobenzenesulfonyl chloride, 4-nitrobenzenesulfonyl chloride, 4-thioamidobenzenesulfonyl chloride, 4-trifluoromethylbenzenesulfonyl chloride, 4-trifluoromethoxybenzenesulfonyl chloride, 2,4,6-trimethylbenzenesulfonyl chloride, 2-phenylethanesulfonyl chloride, 2-thiophenesulfonyl chloride, 5-chloro-2-thiophenesulfonyl chloride, 2,5-dichloro-4-thiophenesulfonyl chloride, 2-thiazolesulfonyl chloride, 2-methyl-4-thiazolesulfonyl chloride, 1-methyl-4-imidazolesulfonyl chloride, 1-methyl-4-pyrazolesulfonyl chloride, 5-chloro-1,3-dimethyl-4-pyrazolesulfonyl chloride, 3-pyridinesulfonyl chloride, 2-pyrimidinesulfonyl chloride, and the like. If desired, a sulfonyl fluoride, sulfonyl bromide or sulfonic acid anhydride may be used in place of the sulfonyl chloride in the above reaction to form the *N*-sulfonyl amino acids of formula IV.

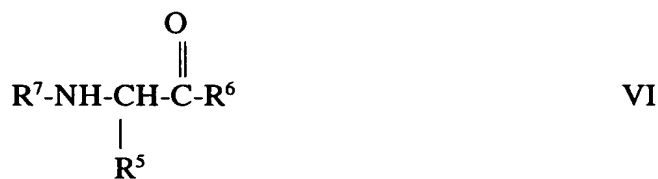
The intermediate *N*-sulfonyl amino acids of formula IV, wherein R^3 and/or R^4 are hydrogen, can also be prepared by reacting a sulfonamide of formula V:



V

wherein R^1 and R^2 are as defined above, with a carboxylic acid derivative of the formula $L(R^3)CHCOOR$ or $L(R^4)CHCOOR$ where L is a leaving group, such as chloro, bromo, iodo, mesylate, tosylate and the like, R^3 or R^4 are as defined above and R is hydrogen or an alkyl group. This reaction is typically conducted by contacting the sulfonamide V with at least one equivalent, preferably 1.1 to 2 equivalents, of the carboxylic acid derivative in the presence of a suitable base, such as triethylamine, in an inert diluent, such as DMF, at a temperature ranging from about 24°C to about 37°C for about 0.5 to about 4 hours. This reaction is further described in Zuckermann et al., *J. Am. Chem. Soc.*, **1992**, *114*, 10646-10647. Preferred carboxylic acid derivatives for use in this reaction are α -chloro and α -bromocarboxylic acid esters such as *tert*-butyl bromoacetate, and the like. When an carboxylic acid ester is employed in this reaction, the ester group is subsequently hydrolyzed using conventional procedures to afford an *N*-sulfonyl amino acid of formula IV.

The compounds of formula I are then prepared by coupling the intermediate *N*-sulfonyl amino acid of formula IV with an amino acid derivative of formula VI:



wherein R^5 - R^7 are as defined above. This coupling reaction is typically conducted using well-known coupling reagents such as carbodiimides, BOP reagent (benzotriazol-1-yloxy-tris(dimethylamino)phosphonium

hexafluorophosphonate) and the like. Suitable carbodiimides include, by way of example, dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) and the like. If desired, polymer supported forms of carbodiimide coupling reagents may also be used including, for example, those described in *Tetrahedron Letters*, **34**(48), 7685 (1993). Additionally, well-known coupling promoters, such as N-hydroxysuccinimide, 1-hydroxybenzotriazole and the like, may be used to facilitate the coupling reaction.

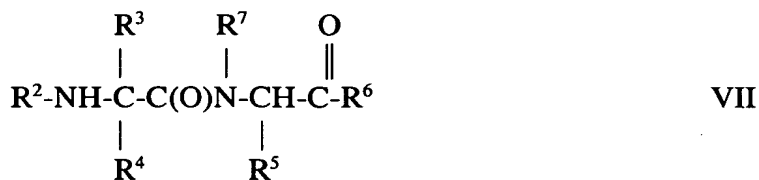
10 This coupling reaction is typically conducted by contacting the *N*-sulfonylamino acid IV with about 1 to about 2 equivalents of the coupling reagent and at least one equivalent, preferably about 1 to about 1.2 equivalents, of amino acid derivative VI in an inert diluent, such as dichloromethane, chloroform, acetonitrile, tetrahydrofuran, *N,N*-
15 dimethylformamide and the like. Generally, this reaction is conducted at a temperature ranging from about 0°C to about 37°C for about 12 to about 24 hours. Upon completion of the reaction, the compound of formula I is recovered by conventional methods including neutralization, extraction, precipitation, chromatography, filtration, and the like.

20 Alternatively, the *N*-sulfonyl amino acid IV can be converted into an acid halide and the acid halide coupled with amino acid derivative VI to provide compounds of formula I. The acid halide of VI can be prepared by contacting VI with an inorganic acid halide, such as thionyl chloride,
25 phosphorous trichloride, phosphorous tribromide or phosphorous pentachloride, or preferably, with oxalyl chloride under conventional conditions. Generally, this reaction is conducted using about 1 to 5 molar equivalents of the inorganic acid halide or oxalyl chloride, either neat or in an inert solvent, such as dichloromethane or carbon tetrachloride, at
30 temperature in the range of about 0°C to about 80°C for about 1 to about 48

hours. A catalyst, such as *N,N*-dimethylformamide, may also be used in this reaction.

The acid halide of *N*-sulfonyl amino acid IV is then contacted with at least one equivalent, preferably about 1.1 to about 1.5 equivalents, of amino acid derivative VI in an inert diluent, such as dichloromethane, at a temperature ranging from about -70°C to about 40°C for about 1 to about 24 hours. Preferably, this reaction is conducted in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, tertiary amines, such as triethylamine, diisopropylethylamine, *N*-methylmorpholine and the like. Alternatively, the reaction can be conducted under Schotten-Baumann-type conditions using aqueous alkali, such as sodium hydroxide and the like. Upon completion of the reaction, the compound of formula I is recovered by conventional methods including neutralization, extraction, precipitation, chromatography, filtration, and the like.

Alternatively, the compounds of formula I can be prepared by first forming a diamino acid derivative of formula VII:



wherein $\text{R}^2\text{-R}^7$ are as defined above. The diamino acid derivatives of formula VII can be readily prepared by coupling an amino acid of formula II with an amino acid derivative of formula VI using conventional amino acid coupling techniques and reagents, such carbodiimides, BOP reagent and the like, as described above. Diamino acid VII can then be sulfonated using a

sulfonyl chloride of formula III and using the synthetic procedures described above to provide a compound of formula I.

5 The amino acid derivatives of formula VI employed in the above reactions are either known compounds or compounds that can be prepared from known compounds by conventional synthetic procedures. For example, amino acid derivatives of formula VI can be prepared by C-alkylating commercially available diethyl 2-acetamidomalonate (Aldrich, Milwaukee, Wisconsin, USA) with an alkyl or substituted alkyl halide. This reaction is typically conducted by treating the diethyl 2-acetamidomalonate with at least one equivalent of sodium ethoxide and at least one equivalent of an alkyl or substituted alkyl halide in refluxing ethanol for about 6 to about 12 hours. The resulting C-alkylated malonate is then deacetylated, hydrolyzed and decarboxylated by heating in aqueous hydrochloric acid at reflux for about 6 to about 12 hours to provide the amino acid, typically as the hydrochloride salt.

Examples of amino acid derivatives of formula VI suitable for use in the above reactions include, but are not limited to, L-alanine methyl ester, L-isoleucine methyl ester, L-leucine methyl ester, L-valine methyl ester, β -*tert*-butyl-L-aspartic acid methyl ester, L-asparagine *tert*-butyl ester, ϵ -Boc-L-lysine methyl ester, ϵ -Cbz-L-lysine methyl ester, γ -*tert*-butyl-L-glutamic acid methyl ester, L-glutamine *tert*-butyl ester, L-(*N*-methyl)histidine methyl ester, L-(*N*-benzyl)histidine methyl ester, L-methionine methyl ester, L-(*O*-benzyl)serine methyl ester, L-tryptophan methyl ester, L-phenylalanine methyl ester, L-phenylalanine isopropyl ester, L-phenylalanine benzyl ester, L-phenylalaninamide, *N*-methyl-L-phenylalanine benzyl ester, 3-carboxy-D,L-phenylalanine methyl ester, 4-carboxy-D,L-phenylalanine methyl ester, L-4-chlorophenylalanine methyl ester, L-4-(3-dimethylaminopropoxy)phenylalanine methyl ester, L-4-iodophenylalanine methyl ester, L-3,4-methylenedioxyphenylalanine methyl ester, L-3,4-

ethylenedioxyphenylalanine methyl ester, L-4-nitrophenylalanine methyl ester, L-tyrosine methyl ester, D,L-homophenylalanine methyl ester, L-(*O*-methyl)tyrosine methyl ester, L-(*O-tert*-butyl)tyrosine methyl ester, L-(*O*-benzyl)tyrosine methyl ester, L-3,5-diiodotyrosine methyl ester, L-3-iodotyrosine methyl ester, β -(1-naphthyl)-L-alanine methyl ester, β -(2-naphthyl)-L-alanine methyl ester, β -(2-thienyl)-L-alanine methyl ester, β -cyclohexyl-L-alanine methyl ester, β -(2-pyridyl)-L-alanine methyl ester, β -(3-pyridyl)-L-alanine methyl ester, β -(4-pyridyl)-L-alanine methyl ester, β -(2-thiazolyl)-D,L-alanine methyl ester, β -(1,2,4-triazol-3-yl)-D,L-alanine methyl ester, and the like. If desired, of course, other esters or amides of the above-described compounds may also be employed.

For ease of synthesis, the compounds of formula I are typically prepared as an ester, i.e., where R⁶ is an alkoxy or substituted alkoxy group and the like. If desired, the ester group can be hydrolysed using conventional conditions and reagents to provide the corresponding carboxylic acid. Typically, this reaction is conducted by treating the ester with at least one equivalent of an alkali metal hydroxide, such as lithium, sodium or potassium hydroxide, in an inert diluent, such as methanol or mixtures of methanol and water, at a temperature ranging about 0°C to about 24°C for about 1 to about 12 hours. Alternatively, benzyl esters may be removed by hydrogenolysis using a palladium catalyst, such as palladium on carbon. The resulting carboxylic acids may be coupled, if desired, to amines such as β -alanine ethyl ester, hydroxyamines such as hydroxylamine and *N*-hydroxysuccinimide, alkoxyamines and substituted alkoxyamines such as *O*-methylhydroxylamine and *O*-benzylhydroxylamine, and the like, using conventional coupling reagents and conditions as described above.

As will be apparent to those skilled in the art, other functional groups present on any of the substituents of the compounds of formula I can be readily modified or derivatized either before or after the above-described

coupling reactions using well-known synthetic procedures. For example, a nitro group present on a substituent of a compound of formula I or an intermediate thereof may be readily reduced by hydrogenation in the presence of a palladium catalyst, such as palladium on carbon, to provide the corresponding amino group. This reaction is typically conducted at a temperature of from about 20°C to about 50°C for about 6 to about 24 hours in an inert diluent, such as methanol. Compounds having a nitro group on the R⁵ substituent can be prepared, for example, by using a 4-nitrophenylalanine derivative and the like in the above-described coupling reactions.

Similarly, a pyridyl group can be hydrogenated in the presence of a platinum catalyst, such as platinum oxide, in an acidic diluent to provide the corresponding piperidinyl analogue. Generally, this reaction is conducted by treating the pyridine compound with hydrogen at a pressure ranging from about 20 psi to about 60 psi, preferably about 40 psi, in the presence of the catalyst at a temperature of about 20°C to about 50°C for about 2 to about 24 hours in an acidic diluent, such as a mixture of methanol and aqueous hydrochloric acid. Compounds having a pyridyl group can be readily prepared by using, for example, β -(2-pyridyl)-, β -(3-pyridyl)- or β -(4-pyridyl)-L-alanine derivatives in the above-described coupling reactions.

Additionally, when the R⁵ substituent of a compound of formula I or an intermediate thereof contains a primary or secondary amino group, such amino groups can be further derivatized either before or after the above coupling reactions to provide, by way of example, amides, sulfonamides, ureas, thioureas, carbamates, secondary or tertiary amines and the like. Compounds having a primary amino group on the R⁵ substituent may be prepared, for example, by reduction of the corresponding nitro compound as described above. Alternatively, such compounds can be prepared by using

an amino acid derivative of formula VI derived from lysine, 4-aminophenylalanine and the like in the above-described coupling reactions.

By way of illustration, a compound of formula I or an intermediate thereof having a substituent containing a primary or secondary amino group, such as where R⁵ is a (4-aminophenyl)methyl group, can be readily *N*-acylated using conventional acylating reagents and conditions to provide the corresponding amide. This acylation reaction is typically conducted by treating the amino compound with at least one equivalent, preferably about 1.1 to about 1.2 equivalents, of a carboxylic acid in the presence of a coupling reagent such as a carbodiimide, BOP reagent (benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphonate) and the like, in an inert diluent, such as dichloromethane, chloroform, acetonitrile, tetrahydrofuran, *N,N*-dimethylformamide and the like, at a temperature ranging from about 0°C to about 37°C for about 4 to about 24 hours. Preferably, a promoter, such as *N*-hydroxysuccinimide, 1-hydroxy-benzotriazole and the like, is used to facilitate the acylation reaction. Examples of carboxylic acids suitable for use in this reaction include, but are not limited to, *N*-*tert*-butyloxycarbonylglycine, *N*-*tert*-butyloxycarbonyl-L-phenylalanine, *N*-*tert*-butyloxycarbonyl-L-aspartic acid benzyl ester, benzoic acid, *N*-*tert*-butyloxycarbonylisonipecotic acid, *N*-methylisonipecotic acid, *N*-*tert*-butyloxycarbonylnipecotic acid, *N*-*tert*-butyloxycarbonyl-L-tetrahydroisoquinoline-3-carboxylic acid, *N*-(toluene-4-sulfonyl)-L-proline and the like.

25

Alternatively, a compound of formula I or an intermediate thereof containing a primary or secondary amino group can be *N*-acylated using an acyl halide or a carboxylic acid anhydride to form the corresponding amide. This reaction is typically conducted by contacting the amino compound with at least one equivalent, preferably about 1.1 to about 1.2 equivalents, of the acyl halide or carboxylic acid anhydride in an inert diluent, such as

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dichloromethane, at a temperature ranging from about of about -70°C to about 40°C for about 1 to about 24 hours. If desired, an acylation catalyst such as 4-(*N,N*-dimethylamino)pyridine may be used to promote the acylation reaction. The acylation reaction is preferably conducted in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, tertiary amines, such as triethylamine, diisopropylethylamine, *N*-methylnmorpholine and the like. Alternatively, the reaction can be conducted under Schotten-Baumann-type conditions using aqueous alkali, such as sodium hydroxide and the like.

Examples of acyl halides and carboxylic acid anhydrides suitable for use in this reaction include, but are not limited to, 2-methylpropionyl chloride, trimethylacetyl chloride, phenylacetyl chloride, benzoyl chloride, 2-bromobenzoyl chloride, 2-methylbenzoyl chloride, 2-trifluoromethylbenzoyl chloride, isonicotinoyl chloride, nicotinoyl chloride, picolinoyl chloride, acetic anhydride, succinic anhydride, and the like. Carbamyl chlorides, such as *N,N*-dimethylcarbamyl chloride, *N,N*-diethylcarbamyl chloride and the like, can also be used in this reaction to provide ureas. Similarly, dicarbonates, such as di-*tert*-butyl dicarbonate, may be employed to provide carbamates.

In a similar manner, a compound of formula I or an intermediate thereof containing a primary or secondary amino group may be *N*-sulfonated to form a sulfonamide using a sulfonyl halide or a sulfonic acid anhydride. Sulfonyl halides and sulfonic acid anhydrides suitable for use in this reaction include, but are not limited to, methanesulfonyl chloride, chloromethanesulfonyl chloride, *p*-toluenesulfonyl chloride, trifluoromethanesulfonic anhydride, and the like. Similarly, sulfamoyl chlorides, such as dimethylsulfamoyl chloride, can be used to provide sulfamides (e.g., >N-SO₂-N<).

Additionally, a primary and secondary amino group present on a substituent of a compound of formula I or an intermediate thereof can be reacted with an isocyanate or a thioisocyanate to give a urea or thiourea, respectively. This reaction is typically conducted by contacting the amino compound with at least one equivalent, preferably about 1.1 to about 1.2 equivalents, of the isocyanate or thioisocyanate in an inert diluent, such as toluene and the like, at a temperature ranging from about 24°C to about 37°C for about 12 to about 24 hours. The isocyanates and thioisocyanates used in this reaction are commercially available or can be prepared from commercially available compounds using well-known synthetic procedures. For example, isocyanates and thioisocyanates are readily prepared by reacting the appropriate amine with phosgene or thiophosgene. Examples of isocyanates and thioisocyanates suitable for use in this reaction include, but are not limited to, ethyl isocyanate, *n*-propyl isocyanate, 4-cyanophenyl isocyanate, 3-methoxyphenyl isocyanate, 2-phenylethyl isocyanate, methyl thioisocyanate, ethyl thioisocyanate, 2-phenylethyl thioisocyanate, 3-phenylpropyl thioisocyanate, 3-(*N,N*-diethylamino)propyl thioisocyanate, phenyl thioisocyanate, benzyl thioisocyanate, 3-pyridyl thioisocyanate, fluorescein isothiocyanate (isomer I) and the like.

Furthermore, when a compound of formula I or an intermediate thereof contains a primary or secondary amino group, the amino group can be reductively alkylated using aldehydes or ketones to form a secondary or tertiary amino group. This reaction is typically conducted by contacting the amino compound with at least one equivalent, preferably about 1.1 to about 1.5 equivalents, of an aldehyde or ketone and at least one equivalent based on the amino compound of a metal hydride reducing agent, such as sodium cyanoborohydride, in an inert diluent, such as methanol, tetrahydrofuran, mixtures thereof and the like, at a temperature ranging from about 0°C to about 50°C for about 1 to about 72 hours. Aldehydes and ketones suitable

for use in this reaction include, by way of example, benzaldehyde, 4-chlorobenzaldehyde, valeraldehyde and the like.

5 In a similar manner, when a compound of formula I or an intermediate thereof has a substituent containing a hydroxyl group, the hydroxyl group can be further modified or derivatized either before or after the above coupling reactions to provide, by way of example, ethers, carbamates and the like. Compounds having a hydroxyl group on the R⁵ substituent, for example, can be prepared using an amino acid derivative of
10 formula VI derived from tyrosine and the like in the above-described reactions.

By way of example, a compound of formula I or an intermediate thereof having a substituent containing a hydroxyl group, such as where R⁵
15 is a (4-hydroxyphenyl)methyl group, can be readily *O*-alkylated to form ethers. This *O*-alkylation reaction is typically conducted by contacting the hydroxy compound with a suitable alkali or alkaline earth metal base, such as potassium carbonate, in an inert diluent, such as acetone, 2-butanone and the like, to form the alkali or alkaline earth metal salt of the hydroxyl group.
20 This salt is generally not isolated, but is reacted *in situ* with at least one equivalent of an alkyl or substituted alkyl halide or sulfonate, such as an alkyl chloride, bromide, iodide, mesylate or tosylate, to afford the ether. Generally, this reaction is conducted at a temperature ranging from about 60°C to about 150°C for about 24 to about 72 hours. Preferably, a catalytic
25 amount of sodium or potassium iodide is added to the reaction mixture when an alkyl chloride or bromide is employed in the reaction.

Examples of alkyl or substituted alkyl halides and sulfonates suitable for use in this reaction include, but are not limited to, *tert*-butyl
30 bromoacetate, *N-tert*-butyl chloroacetamide, 1-bromoethylbenzene, ethyl α -bromophenylacetate, 2-(*N*-ethyl-*N*-phenylamino)ethyl chloride, 2-(*N,N*-

ethylamino)ethyl chloride, 2-(*N,N*-diisopropylamino)ethyl chloride, 2-(*N,N*-dibenzylamino)ethyl chloride, 3-(*N,N*-ethylamino)propyl chloride, 3-(*N*-benzyl-*N*-methylamino)propyl chloride, *N*-(2-chloroethyl)morpholine, 2-(hexamethyleneimino)ethyl chloride, 3-(*N*-methylpiperazine)propyl chloride, 1-(3-chlorophenyl)-4-(3-chloropropyl)piperazine, 2-(4-hydroxy-4-phenylpiperidine)ethyl chloride, *N-tert*-butyloxycarbonyl-3-piperidinemethyl tosylate, and the like.

Alternatively, a hydroxyl group present on a substituent of a compound of formula I or an intermediate thereof can be *O*-alkylating using the Mitsunobu reaction. In this reaction, an alcohol, such as 3-(*N,N*-dimethylamino)-1-propanol and the like, is reacted with about 1.0 to about 1.3 equivalents of triphenylphosphine and about 1.0 to about 1.3 equivalents of diethyl azodicarboxylate in an inert diluent, such as tetrahydrofuran, at a temperature ranging from about -10°C to about 5°C for about 0.25 to about 1 hour. About 1.0 to about 1.3 equivalents of a hydroxy compound, such as *N-tert*-butyltyrosine methyl ester, is then added and the reaction mixture is stirred at a temperature of about 0°C to about 30°C for about 2 to about 48 hours to provide the *O*-alkylated product.

In a similar manner, a compound of formula I or an intermediate thereof containing a aryl hydroxy group can be reacted with an aryl iodide to provide a diaryl ether. Generally, this reaction is conducted by forming the alkali metal salt of the hydroxyl group using a suitable base, such as sodium hydride, in an inert diluent such as xylenes at a temperature of about -25°C to about 10°C. The salt is then treated with about 1.1 to about 1.5 equivalents of cuprous bromide dimethyl sulfide complex at a temperature ranging from about 10°C to about 30°C for about 0.5 to about 2.0 hours, followed by about 1.1 to about 1.5 equivalents of an aryl iodide, such as sodium 2-iodobenzoate and the like. The reaction is then heated to about

70°C to about 150°C for about 2 to about 24 hours to provide the diaryl ether.

5 Additionally, a hydroxy-containing compound can also be readily
derivatized to form a carbamate. In one method for preparing such
carbamates, a hydroxy compound of formula I or an intermediate thereof is
contacted with about 1.0 to about 1.2 equivalents of 4-nitrophenyl
chloroformate in an inert diluent, such as dichloromethane, at a temperature
ranging from about -25°C to about 0°C for about 0.5 to about 2.0 hours.
10 Treatment of the resulting carbonate with an excess, preferably about 2 to
about 5 equivalents, of a trialkylamine, such as triethylamine, for about 0.5
to 2 hours, followed by about 1.0 to about 1.5 equivalents of a primary or
secondary amine provides the carbamate. Examples of amines suitable for
using in this reaction include, but are not limited to, piperazine, 1-
15 methylpiperazine, 1-acetylpiperazine, morpholine, thiomorpholine,
pyrrolidine, piperidine and the like.

 Alternatively, in another method for preparing carbamates, a
hydroxy-containing compound is contacted with about 1.0 to about 1.5
20 equivalents of a carbamyl chloride in an inert diluent, such as
dichloromethane, at a temperature ranging from about 25°C to about 70°C
for about 2 to about 72 hours. Typically, this reaction is conducted in the
presence of a suitable base to scavenge the acid generated during the
reaction. Suitable bases include, by way of example, tertiary amines, such
25 as triethylamine, diisopropylethylamine, *N*-methylethanolamine and the like.
Additionally, at least one equivalent (based on the hydroxy compound) of 4-
(*N,N*-dimethylamino)pyridine is preferably added to the reaction mixture to
facilitate the reaction. Examples of carbamyl chlorides suitable for use in
this reaction include, by way of example, dimethylcarbamyl chloride,
30 diethylcarbamyl chloride and the like.

Likewise, when a compound of formula I or an intermediate thereof contains a primary or secondary hydroxyl group, such hydroxyl groups can be readily converted into a leaving group and displaced to form, for example, amines, sulfides and fluorides. For example, derivatives of 4-
5 hydroxy-L-proline can be converted into the corresponding 4-amino, 4-thio or 4-fluoro-L-proline derivatives via nucleophilic displacement of the derivatized hydroxyl group. Generally, when a chiral compound is employed in these reactions, the stereochemistry at the carbon atom attached to the derivatized hydroxyl group is typically inverted.

10

These reactions are typically conducted by first converting the hydroxyl group into a leaving group, such as a tosylate, by treatment of the hydroxy compound with at least one equivalent of a sulfonyl halide, such as *p*-toluenesulfonyl chloride and the like, in pyridine. This reaction is
15 generally conducted at a temperature of from about 0°C to about 70°C for about 1 to about 48 hours. The resulting tosylate can then be readily displaced with sodium azide, for example, by contacting the tosylate with at least one equivalent of sodium azide in an inert diluent, such as a mixture of *N,N*-dimethylformamide and water, at a temperature ranging from about 0°C
20 to about 37°C for about 1 to about 12 hours to provide the corresponding azido compound. The azido group can then be reduced by, for example, hydrogenation using a palladium on carbon catalyst to provide the amino (-NH₂) compound.

25 Similarly, a tosylate group can be readily displaced by a thiol to form a sulfide. This reaction is typically conducted by contacting the tosylate with at least one equivalent of a thiol, such as thiophenol, in the presence of a suitable base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), in an inert diluent, such as *N,N*-dimethylformamide, at a temperature of from about
30 0°C to about 37°C for about 1 to about 12 hours to provide the sulfide. Additionally, treatment of a tosylate with morpholinosulfur trifluoride in an

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inert diluent, such as dichloromethane, at a temperature ranging from about 0°C to about 37°C for about 12 to about 24 hours affords the corresponding fluoro compound.

5 Furthermore, a compound of formula I or an intermediate thereof having a substituent containing an iodoaryl group, for example, when R⁵ is a (4-iodophenyl)methyl group, can be readily converted either before or after the above coupling reactions into a biaryl compound. Typically, this reaction is conducted by treating the iodoaryl compound with about 1.1 to
10 about 2 equivalents of an arylzinc iodide, such as 2-(methoxycarbonyl)phenylzinc iodide, in the presence of a palladium catalyst, such as palladium tetra(triphenylphosphine), in an inert diluent, such as tetrahydrofuran, at a temperature ranging from about 24°C to about 30°C until reaction completion. This reaction is further described, for example, in
15 Rieke, *J. Org. Chem.* **1991**, 56, 1445.

In some cases, the compounds of formula I or intermediates thereof may contain substituents having one or more sulfur atoms. Such sulfur atoms will be present, for example, when the amino acid of formula II
20 employed in the above reactions is derived from L-thiazolidine-4-carboxylic acid, L-(5,5-dimethyl)thiazolidine-4-carboxylic acid, L-thiamorpholine-3-carboxylic acid and the like. When present, such sulfur atoms can be oxidized either before or after the above coupling reactions to provide a sulfoxide or sulfone compound using conventional reagents and reaction
25 conditions. Suitable reagents for oxidizing a sulfide compound to a sulfoxide include, by way of example, hydrogen peroxide, 3-chloroperoxybenzoic acid (MCPBA), sodium periodate and the like. The oxidation reaction is typically conducted by contacting the sulfide compound with about 0.95 to about 1.1 equivalents of the oxidizing reagent in an inert diluent, such as
30 dichloromethane, at a temperature ranging from about -50°C to about 75°C for about 1 to about 24 hours. The resulting sulfoxide can then be further

oxidized to the corresponding sulfone by contacting the sulfoxide with at least one additional equivalent of an oxidizing reagent, such as hydrogen peroxide, MCPBA, potassium permanganate and the like. Alternatively, the sulfone can be prepared directly by contacting the sulfide with at least two equivalents, and preferably an excess, of the oxidizing reagent. Such reactions are described further in March, "Advanced Organic Chemistry", 4th Ed., pp. 1201-1202, Wiley Publisher, 1992.

As described above, the compounds of formula I having an R² substituent other than hydrogen can be prepared using an N-substituted amino acid of formula II, such as sarcosine, N-methyl-L-phenylalanine and the like, in the above-described coupling reactions. Alternatively, such compounds can be prepared by N-alkylation of a sulfonamide of formula I or IV (where R² is hydrogen) using conventional synthetic procedures. Typically, this N-alkylation reaction is conducted by contacting the sulfonamide with at least one equivalent, preferably 1.1 to 2 equivalents, of an alkyl or substituted alkyl halide in the presence of a suitable base, such as potassium carbonate, in an inert diluent, such as acetone, 2-butanone and the like, at a temperature ranging from about 25°C to about 70°C for about 2 to about 48 hours. Examples of alkyl or substituted alkyl halides suitable for use in this reaction include, but are not limited to, methyl iodide, and the like.

Additionally, the sulfonamides of formula I or IV wherein R² is hydrogen and R¹ is a 2-alkoxycarbonylaryl group can be intramolecularly cyclized to form 1,2-benzisothiazol-3-one derivatives or analogues thereof. This reaction is typically conducted by treating a sulfonamide, such as N-(2-methoxycarbonylphenylsulfonyl)glycine-L-phenylalanine benzyl ester, with about 1.0 to 1.5 equivalents of a suitable base, such as an alkali metal hydride, in an inert diluent, such as tetrahydrofuran, at a temperature ranging from about 0°C to about 30°C for about 2 to about 48 hours to afford the cyclized 1,2-benzisothiazol-3-one derivative.

Lastly, the compounds of formula I where Q is $-C(S)NR^7-$ are can prepared by using an amino thionoacid derivative in place of amino acid II in the above described synthetic procedures. Such amino thionoacid derivatives can be prepared by the procedures described in Shalaky, et al., *J. Org.*

5 *Chem.*, 61:9045-9048 (1996) and Brain, et al., *J. Org. Chem.*, 62:3808-3809 (1997) and references cited therein.

Pharmaceutical Formulations

When employed as pharmaceuticals, the compounds of formula I and
10 IA are usually administered in the form of pharmaceutical compositions. These compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. These compounds are effective as both injectable and oral compositions. Such compositions are prepared in a manner well known in
15 the pharmaceutical art and comprise at least one active compound.

This invention also includes pharmaceutical compositions which contain, as the active ingredient, one or more of the compounds of formula I and IA above associated with pharmaceutically acceptable carriers. In
20 making the compositions of this invention, the active ingredient is usually mixed with an excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the
25 active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and
30 sterile packaged powders.

In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxybenzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 100 mg, more usually about 10 to about 30 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

The active compound is effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It, will be understood, however, that the amount of the compound actually administered

will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

5

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of the present invention.

15

The tablets or pills of the present invention may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

20

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The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions suitably flavored syrups, aqueous or oil

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suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

5 Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. Preferably the compositions are administered by the oral or nasal respiratory
10 route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face masks tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder
15 compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

 The following formulation examples illustrate the pharmaceutical compositions of the present invention.

20

Formulation Example 1

 Hard gelatin capsules containing the following ingredients are prepared:

25	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/capsule)</u>
	Active Ingredient	30.0
	Starch	305.0
30	Magnesium stearate	5.0

 The above ingredients are mixed and filled into hard gelatin capsules in 340 mg quantities.

Formulation Example 2

A tablet formula is prepared using the ingredients below:

	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/tablet)</u>
5	Active Ingredient	25.0
	Cellulose, microcrystalline	200.0
	Colloidal silicon dioxide	10.0
	Stearic acid	5.0

10

The components are blended and compressed to form tablets, each weighing 240 mg.

Formulation Example 3

15 A dry powder inhaler formulation is prepared containing the following components:

	<u>Ingredient</u>	<u>Weight %</u>
20	Active Ingredient	5
	Lactose	95

25 The active mixture is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.

Formulation Example 4

Tablets, each containing 30 mg of active ingredient, are prepared as follows:

	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/tablet)</u>
30	Active Ingredient	30.0 mg
	Starch	45.0 mg
35	Microcrystalline cellulose	35.0 mg
	Polyvinylpyrrolidone (as 10% solution in water)	4.0 mg
	Sodium carboxymethyl starch	4.5 mg
	Magnesium stearate	0.5 mg

Talc	<u>1.0 mg</u>
Total	120 mg

5 The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50° to 60°C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation Example 5

15 Capsules, each containing 40 mg of medicament are made as follows:

<u>Ingredient</u>	<u>Quantity</u> <u>(mg/capsule)</u>
Active Ingredient	40.0 mg
Starch	109.0 mg
Magnesium stearate	<u>1.0 mg</u>
Total	150.0 mg

25 The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 150 mg quantities.

Formulation Example 6

30 Suppositories, each containing 25 mg of active ingredient are made as follows:

<u>Ingredient</u>	<u>Amount</u>
Active Ingredient	25 mg
Saturated fatty acid glycerides to	2,000 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository
5 mold of nominal 2.0 g capacity and allowed to cool.

Formulation Example 7

10 Suspensions, each containing 50 mg of medicament per 5.0 ml dose are made as follows:

	<u>Ingredient</u>	<u>Amount</u>
15	Active Ingredient	50.0 mg
	Xanthan gum	4.0 mg
	Sodium carboxymethyl cellulose (11 %)	
	Microcrystalline cellulose (89 %)	50.0 mg
	Sucrose	1.75 g
20	Sodium benzoate	10.0 mg
	Flavor and Color	q.v.
	Purified water to	5.0 ml

25 The medicament, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and color are diluted with some of the water and added with stirring. Sufficient water is then added to produce the
30 required volume.

Formulation Example 8

	<u>Ingredient</u>	<u>Quantity (mg/capsule)</u>
35	Active Ingredient	15.0 mg
	Starch	407.0 mg

Magnesium stearate	<u>3.0 mg</u>
Total	425.0 mg

5 The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 560 mg quantities.

Formulation Example 9

10 An intravenous formulation may be prepared as follows:

	<u>Ingredient</u>	<u>Quantity</u>
	Active Ingredient	250.0 mg
15	Isotonic saline	1000 ml

Formulation Example 10

A topical formulation may be prepared as follows:

	<u>Ingredient</u>	<u>Quantity</u>
20	Active Ingredient	1-10 g
	Emulsifying Wax	30 g
	Liquid Paraffin	20 g
	White Soft Paraffin	to 100 g

25

30 The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The active ingredient is added and stirring is continued until dispersed. The mixture is then cooled until solid.

35 Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Patent

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5,023,252, issued June 11, 1991, herein incorporated by reference. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

5 Direct or indirect placement techniques may be used when it is desirable or necessary to introduce the pharmaceutical composition to the brain. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system used for the transport of biological factors to
10 specific anatomical regions of the body is described in U.S. Patent 5,011,472 which is herein incorporated by reference.

Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentiation by the
15 conversion of hydrophilic drugs into lipid-soluble drugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced by
20 intra-arterial infusion of hypertonic solutions which can transiently open the blood-brain barrier.

Utility

25 The compounds of this invention can be employed to bind VLA-4 ($\alpha_4\beta_1$ integrin) in biological samples and, accordingly have utility in, for example, assaying such samples for VLA-4. In such assays, the compounds can be bound to a solid support and the VLA-4 sample added thereto. The amount of VLA-4 in the sample can be determined by conventional methods such as use of a sandwich ELISA assay. Alternatively, labeled VLA-4 can be used
30 in a competitive assay to measure for the presence of VLA-4 in the sample. Other suitable assays are well known in the art.

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In addition, certain of the compounds of this invention inhibit, *in vivo*, adhesion of leukocytes to endothelial cells mediated by VLA-4 and, accordingly, can be used in the treatment of diseases mediated by VLA-4. Such diseases include inflammatory diseases in mammalian patients
5 such as asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes (including acute juvenile onset diabetes), inflammatory bowel disease (including ulcerative colitis and Crohn's disease), multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis, meningitis, encephalitis, stroke, and other cerebral traumas, nephritis, retinitis, atopic
10 dermatitis, psoriasis, myocardial ischemia and acute leukocyte-mediated lung injury such as that which occurs in adult respiratory distress syndrome.

The biological activity of the compounds identified above may be assayed in a variety of systems. For example, a compound can be
15 immobilized on a solid surface and adhesion of cells expressing VLA-4 can be measured. Using such formats, large numbers of compounds can be screened. Cells suitable for this assay include any leukocytes known to express VLA-4 such as T cells, B cells, monocytes, eosinophils, and basophils. A number of leukocyte cell lines can also be used, examples
20 include Jurkat and U937.

The test compounds can also be tested for the ability to competitively inhibit binding between VLA-4 and VCAM-1, or between VLA-4 and a labeled compound known to bind VLA-4 such as a compound of this
25 invention or antibodies to VLA-4. In these assays, the VCAM-1 can be immobilized on a solid surface. VCAM-1 may also be expressed as a recombinant fusion protein having an Ig tail (e.g., IgG) so that binding to VLA-4 may be detected in an immunoassay. Alternatively, VCAM-1 expressing cells, such as activated endothelial cells or VCAM-1 transfected
30 fibroblasts can be used. For assays to measure the ability to block adhesion to brain endothelial cells, the assays described in International Patent

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Application Publication No. WO 91/05038 are particularly preferred. This application is incorporated herein by reference in its entirety.

Many assay formats employ labelled assay components. The labelling systems can be in a variety of forms. The label may be coupled directly or indirectly to the desired component of the assay according to methods well known in the art. A wide variety of labels may be used. The component may be labelled by any one of several methods. The most common method of detection is the use of autoradiography with ^3H , ^{125}I , ^{35}S , ^{14}C , or ^{32}P labelled compounds or the like. Non-radioactive labels include ligands which bind to labelled antibodies, fluorophores, chemiluminescent agents, enzymes and antibodies which can serve as specific binding pair members for a labelled ligand. The choice of label depends on sensitivity required, ease of conjugation with the compound, stability requirements, and available instrumentation.

Appropriate *in vivo* models for demonstrating efficacy in treating inflammatory responses include EAE (experimental autoimmune encephalomyelitis) in mice, rats, guinea pigs or primates, as well as other inflammatory models dependent upon $\alpha 4$ integrins.

Compounds having the desired biological activity may be modified as necessary to provide desired properties such as improved pharmacological properties (e.g., *in vivo* stability, bio-availability), or the ability to be detected in diagnostic applications. For instance, inclusion of one or more D-amino acids in the sulfonamides of this invention typically increases *in vivo* stability. Stability can be assayed in a variety of ways such as by measuring the half-life of the proteins during incubation with peptidases or human plasma or serum. A number of such protein stability assays have been described (see, e.g., Verhoef et al., Eur. J. Drug Metab. Pharmacokinet., 1990, 15(2):83-93).

For diagnostic purposes, a wide variety of labels may be linked to the compounds, which may provide, directly or indirectly, a detectable signal. Thus, the compounds of the subject invention may be modified in a variety of ways for a variety of end purposes while still retaining biological activity.

5 In addition, various reactive sites may be introduced at the terminus for linking to particles, solid substrates, macromolecules, or the like.

Labeled compounds can be used in a variety of *in vivo* or *in vitro* applications. A wide variety of labels may be employed, such as
10 radionuclides (e.g., gamma-emitting radioisotopes such as technetium-99 or indium-111), fluorescers (e.g., fluorescein), enzymes, enzyme substrates, enzyme cofactors, enzyme inhibitors, chemiluminescent compounds, bioluminescent compounds, and the like. Those of ordinary skill in the art will know of other suitable labels for binding to the complexes, or will be
15 able to ascertain such using routine experimentation. The binding of these labels is achieved using standard techniques common to those of ordinary skill in the art.

In vitro uses include diagnostic applications such as monitoring
20 inflammatory responses by detecting the presence of leukocytes expressing VLA-4. The compounds of this invention can also be used for isolating or labeling such cells. In addition, as mentioned above, the compounds of the invention can be used to assay for potential inhibitors of VLA-4/VCAM-1 interactions.

25

For *in vivo* diagnostic imaging to identify, e.g., sites of inflammation, radioisotopes are typically used in accordance with well known techniques. The radioisotopes may be bound to the peptide either directly or indirectly using intermediate functional groups. For instance, chelating agents such as
30 diethylenetriaminepentacetic acid (DTPA) and ethylenediaminetetraacetic

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acid (EDTA) and similar molecules have been used to bind proteins to metallic ion radioisotopes.

5 The complexes can also be labeled with a paramagnetic isotope for purposes of *in vivo* diagnosis, as in magnetic resonance imaging (MRI) or electron spin resonance (ESR), both of which are well known. In general, any conventional method for visualizing diagnostic imaging can be used. Usually gamma- and positron-emitting radioisotopes are used for camera imaging and paramagnetic isotopes are used for MRI. Thus, the compounds
10 can be used to monitor the course of amelioration of an inflammatory response in an individual. By measuring the increase or decrease in lymphocytes expressing VLA-4 it is possible to determine whether a particular therapeutic regimen aimed at ameliorating the disease is effective.

15 The pharmaceutical compositions of the present invention can be used to block or inhibit cellular adhesion associated with a number of diseases and disorders. For instance, a number of inflammatory disorders are associated with integrins or leukocytes. Treatable disorders include, e.g., transplantation rejection (e.g., allograft rejection), Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes (including acute juvenile onset
20 diabetes), retinitis, cancer metastases, rheumatoid arthritis, acute leukocyte-mediated lung injury (e.g., adult respiratory distress syndrome), asthma, nephritis, and acute and chronic inflammation, including atopic dermatitis, psoriasis, myocardial ischemia, and inflammatory bowel disease (including Crohn's disease and ulcerative colitis). In preferred embodiments
25 the pharmaceutical compositions are used to treat inflammatory brain disorders, such as multiple sclerosis (MS), viral meningitis and encephalitis.

Inflammatory bowel disease is a collective term for two similar diseases
30 referred to as Crohn's disease and ulcerative colitis. Crohn's disease is an idiopathic, chronic ulceroconstrictive inflammatory disease characterized by

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sharply delimited and typically transmural involvement of all layers of the bowel wall by a granulomatous inflammatory reaction. Any segment of the gastrointestinal tract, from the mouth to the anus, may be involved, although the disease most commonly affects the terminal ileum and/or colon.

- 5 Ulcerative colitis is an inflammatory response limited largely to the colonic mucosa and submucosa. Lymphocytes and macrophages are numerous in lesions of inflammatory bowel disease and may contribute to inflammatory injury.

- 10 Asthma is a disease characterized by increased responsiveness of the tracheobronchial tree to various stimuli potentiating paroxysmal constriction of the bronchial airways. The stimuli cause release of various mediators of inflammation from IgE-coated mast cells including histamine, eosinophilic and neutrophilic chemotactic factors, leukotrienes, prostaglandin and platelet
15 activating factor. Release of these factors recruits basophils, eosinophils and neutrophils, which cause inflammatory injury.

- Atherosclerosis is a disease of arteries (e.g., coronary, carotid, aorta and iliac). The basic lesion, the atheroma, consists of a raised focal plaque
20 within the intima, having a core of lipid and a covering fibrous cap. Atheromas compromise arterial blood flow and weaken affected arteries. Myocardial and cerebral infarcts are a major consequence of this disease. Macrophages and leukocytes are recruited to atheromas and contribute to inflammatory injury.

25

- Rheumatoid arthritis is a chronic, relapsing inflammatory disease that primarily causes impairment and destruction of joints. Rheumatoid arthritis usually first affects the small joints of the hands and feet but then may involve the wrists, elbows, ankles and knees. The arthritis results from
30 interaction of synovial cells with leukocytes that infiltrate from the

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circulation into the synovial lining of the joints. See *e.g.*, Paul, *Immunology* (3d ed., Raven Press, 1993).

Another indication for the compounds of this invention is in treatment of organ or graft rejection mediated by VLA-4. Over recent years there has been a considerable improvement in the efficiency of surgical techniques for transplanting tissues and organs such as skin, kidney, liver, heart, lung, pancreas and bone marrow. Perhaps the principal outstanding problem is the lack of satisfactory agents for inducing immunotolerance in the recipient to the transplanted allograft or organ. When allogeneic cells or organs are transplanted into a host (i.e., the donor and donee are different individuals from the same species), the host immune system is likely to mount an immune response to foreign antigens in the transplant (host-versus-graft disease) leading to destruction of the transplanted tissue. CD8⁺ cells, CD4 cells and monocytes are all involved in the rejection of transplant tissues. Compounds of this invention which bind to alpha-4 integrin are useful, *inter alia*, to block alloantigen-induced immune responses in the donee thereby preventing such cells from participating in the destruction of the transplanted tissue or organ. See, *e.g.*, Paul et al., *Transplant International* 9, 420-425 (1996); Georczynski et al., *Immunology* 87, 573-580 (1996); Georczynski et al., *Transplant. Immunol.* 3, 55-61 (1995); Yang et al., *Transplantation* 60, 71-76 (1995); Anderson et al., *APMIS* 102, 23-27 (1994).

A related use for compounds of this invention which bind to VLA-4 is in modulating the immune response involved in "graft versus host" disease (GVHD). See *e.g.*, Schlegel et al., *J. Immunol.* 155, 3856-3865 (1995). GVHD is a potentially fatal disease that occurs when immunologically competent cells are transferred to an allogeneic recipient. In this situation, the donor's immunocompetent cells may attack tissues in the recipient. Tissues of the skin, gut epithelia and liver are frequent targets and may be destroyed during the course of GVHD. The disease presents an especially

severe problem when immune tissue is being transplanted, such as in bone marrow transplantation; but less severe GVHD has also been reported in other cases as well, including heart and liver transplants. The therapeutic agents of the present invention are used, *inter alia*, to block activation of the donor T-cells thereby interfering with their ability to lyse target cells in the host.

A further use of the compounds of this invention is inhibiting tumor metastasis. Several tumor cells have been reported to express VLA-4 and compounds which bind VLA-4 block adhesion of such cells to endothelial cells. Steinback et al., *Urol. Res.* 23, 175-83 (1995); Orosz et al., *Int. J. Cancer* 60, 867-71 (1995); Freedman et al., *Leuk. Lymphoma* 13, 47-52 (1994); Okahara et al., *Cancer Res.* 54, 3233-6 (1994).

A further use of the compounds of this invention is in treating multiple sclerosis. Multiple sclerosis is a progressive neurological autoimmune disease that affects an estimated 250,000 to 350,000 people in the United States. Multiple sclerosis is thought to be the result of a specific autoimmune reaction in which certain leukocytes attack and initiate the destruction of myelin, the insulating sheath covering nerve fibers. In an animal model for multiple sclerosis, murine monoclonal antibodies directed against VLA-4 have been shown to block the adhesion of leukocytes to the endothelium, and thus prevent inflammation of the central nervous system and subsequent paralysis in the animals¹⁶.

Pharmaceutical compositions of the invention are suitable for use in a variety of drug delivery systems. Suitable formulations for use in the present invention are found in *Remington's Pharmaceutical Sciences*, Mace Publishing Company, Philadelphia, PA, 17th ed. (1985).

In order to enhance serum half-life, the compounds may be encapsulated, introduced into the lumen of liposomes, prepared as a colloid, or other conventional techniques may be employed which provide an extended serum half-life of the compounds. A variety of methods are available for preparing liposomes, as described in, e.g., Szoka, et al., U.S. Patent Nos. 4,235,871, 4,501,728 and 4,837,028 each of which is incorporated herein by reference.

The amount administered to the patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions are administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. An amount adequate to accomplish this is defined as "therapeutically effective dose." Amounts effective for this use will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the inflammation, the age, weight and general condition of the patient, and the like.

The compositions administered to a patient are in the form of pharmaceutical compositions described above. These compositions may be sterilized by conventional sterilization techniques, or may be sterile filtered. The resulting aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

The therapeutic dosage of the compounds of the present invention will vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. For example, for intravenous administration, the dose will typically be in the range of about 20 μ g to about 500 μ g per kilogram body weight, preferably about 100 μ g to about 300 μ g per kilogram body weight. Suitable dosage ranges for intranasal administration are generally about 0.1 pg to 1 mg per kilogram body weight. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

The following synthetic and biological examples are offered to illustrate this invention and are not to be construed in any way as limiting the scope of this invention. Unless otherwise stated, all temperatures are in degrees Celsius.

EXAMPLES

In the examples below, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

	aq or aq.	=	aqueous
	AcOH	=	acetic acid
	bd	=	broad doublet
25	bm	=	broad multiplet
	bs	=	broad singlet
	Bn	=	benzyl
	Boc	=	<i>N</i> - <i>tert</i> -butoxycarbonyl
	Boc ₂ O	=	di- <i>tert</i> -butyl dicarbonate
30	BOP	=	benzotriazol-1-yloxy- tris(dimethylamino)phosphonium hexafluorophosphate
	Cbz	=	carbobenzyloxy
	CHCl ₃	=	chloroform
35	CH ₂ Cl ₂	=	dichloromethane
	(COCl) ₂	=	oxalyl chloride

	d	=	doublet
	dd	=	doublet of doublets
	dt	=	doublet of triplets
	DBU	=	1,8-diazabicyclo[5.4.0]undec-7-ene
5	DCC	=	1,3-dicyclohexylcarbodiimide
	DMAP	=	4- <i>N,N</i> -dimethylaminopyridine
	DME	=	ethylene glycol dimethyl ether
	DMF	=	<i>N,N</i> -dimethylformamide
	DMSO	=	dimethylsulfoxide
10	EDC	=	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
	Et ₃ N	=	triethylamine
	Et ₂ O	=	diethyl ether
	EtOAc	=	ethyl acetate
15	EtOH	=	ethanol
	eq or eq.	=	equivalent
	Fmoc	=	<i>N</i> -(9-fluorenylmethoxycarbonyl)
	FmocONSu	=	<i>N</i> -(9-fluorenylmethoxycarbonyl)-succinimide
20	g	=	grams
	h	=	hour
	H ₂ O	=	water
	HBr	=	hydrobromic acid
	HCl	=	hydrochloric acid
25	HOBT	=	1-hydroxybenzotriazole hydrate
	hr	=	hour
	K ₂ CO ₃	=	potassium carbonate
	L	=	liter
	m	=	multiple
30	MeOH	=	methanol
	mg	=	milligram
	MgSO ₄	=	magnesium sulfate
	mL	=	milliliter
	mm	=	millimeter
35	mM	=	millimolar
	mmol	=	millimol
	mp	=	melting point
	N	=	normal
	NaCl	=	sodium chloride
40	Na ₂ CO ₃	=	sodium carbonate
	NaHCO ₃	=	sodium bicarbonate
	NaOEt	=	sodium ethoxide
	NaOH	=	sodium hydroxide
	NH ₄ Cl	=	ammonium chloride
45	NMM	=	<i>N</i> -methylmorpholine
	Phe	=	L-phenylalanine

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	Pro	=	L-proline
	psi	=	pounds per square inch
	PtO ₂	=	platinum oxide
	q	=	quartet
5	quint.	=	quintet
	rt	=	room temperature
	s	=	singlet
	sat	=	saturated
	t	=	triplet
10	t-BuOH	=	<i>tert</i> -butanol
	TFA	=	trifluoroacetic acid
	THF	=	tetrahydrofuran
	TLC or tlc	=	thin layer chromatography
	Ts	=	tosyl
15	TsCl	=	tosyl chloride
	TsOH	=	tosylate
	μL	=	microliter

20 In the examples below, all temperatures are in degrees Celcius (unless otherwise indicated). The following Methods were used to prepare the compounds set forth below as indicated.

Method 1

25 N-Tosylation Procedure

N-Tosylation of the appropriate amino acid was conducted via the method of Cupps, Boutin and Rapoport *J. Org. Chem.* **1985**, *50*, 3972.

Method 2

30 Methyl Ester Preparation Procedure

Amino acid methyl esters were prepared using the method of Brenner and Huber *Helv. Chim. Acta* 1953, *36*, 1109.

Method 3

35 BOP Coupling Procedure

The desired dipeptide ester was prepared by the reaction of a suitable N-protected amino acid (1 equivalent) with the appropriate amino acid ester or

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amino acid ester hydrochloride (1 equivalent), benzotriazol-1-yloxy-
tris(dimethylamino)phosphonium hexafluorophosphate [BOP] (2.0
equivalent), triethylamine (1.1 equivalent), and DMF. The reaction mixture
was stirred at room temperature overnight. The crude product is purified
5 flash chromatography to afford the dipeptide ester.

Method 4

Hydrogenation Procedure I

Hydrogenation was performed using 10% palladium on carbon (10% by
10 weight) in methanol at 30 psi overnight. The mixture was filtered through a
pad of Celite and the filtrate concentrated to yield the desired amino
compound.

Method 5

Hydrolysis Procedure I

To a chilled (0°C) THF/H₂O solution (2:1, 5 - 10 mL) of the
appropriate ester was added LiOH (or NaOH) (0.95 equivalents). The
temperature was maintained at 0°C and the reaction was complete in 1-3
hours. The reaction mixture was extracted with ethyl acetate and the
20 aqueous phase was lyophilized resulting in the desired carboxylate salt.

Method 6

Ester Hydrolysis Procedure II

To a chilled (0°C) THF/H₂O solution (2:1, 5 - 10 mL) of the
25 appropriate ester was added LiOH (1.1 equivalents). The temperature was
maintained at 0°C and the reaction was complete in 1-3 hours. The reaction
mixture was concentrated and the residue was taken up into H₂O and the pH
adjusted to 2-3 with aqueous HCl. The product was extracted with ethyl
acetate and the combined organic phase was washed with brine, dried over
30 MgSO₄, filtered and concentrated to yield the desired acid.

Method 7

Ester Hydrolysis Procedure III

5 The appropriate ester was dissolved in dioxane/H₂O (1:1) and 0.9 equivalents of 0.5 N NaOH was added. The reaction was stirred for 3-16 hours and then concentrated. The resulting residue was dissolved in H₂O and extracted with ethyl acetate. The aqueous phase was lyophilized to yield the desired carboxylate sodium salt.

Method 8

10 Sulfonylation Procedure I

To the appropriately protected aminophenylalanine analog (11.2 mmol), dissolved in methylene chloride (25ml) and cooled to -78°C was added the desired sulfonyl chloride (12 mmol) followed by dropwise addition of pyridine (2 mL). The solution was allowed to warm to room temperature and was stirred for 48 hr. The reaction solution was transferred to a 250 mL separatory funnel with methylene chloride (100 mL) and extracted with 1N HCl (50 mL x 3), brine (50 mL), and water (100 mL). The organic phase was dried (MgSO₄) and the solvent concentrated to yield the desired product.

20 Method 9

Reductive Amination Procedure

25 Reductive amination of Tos-Pro-p-NH₂-Phe with the appropriate aldehyde was conducted using acetic acid, sodium triacetoxyborohydride, methylene chloride and the combined mixture was stirred at room temperature overnight. The crude product was purified by flash chromatography.

Method 10

BOC Removal Procedure

30 Anhydrous hydrochloride (HCl) gas was bubbled through a methanolic solution of the appropriate Boc-amino acid ester at 0°C for 15 minutes and

5

Tert-Butyl Ester Hydrolysis Procedure I

10

EDC Coupling Procedure I

15

Method 13

EDC Coupling Procedure II

30

reaction was allowed to rise to room temperature and stirred overnight. The reaction mixture was partitioned between EtOAc and H₂O and the organic phase washed with 0.2 N citric acid, H₂O, sat. NaHCO₃, brine, dried (MgSO₄ or Na₂SO₄), filtered and concentrated. The crude product was purified by column chromatography or preparative TLC.

Method 14

Sulfonylation Procedure II

The appropriate sulfonyl chloride was dissolved in CH₂Cl₂ and placed in an ice bath. L-Pro-L-Phe-OMe \cdot HCl (1 equivalent) and Et₃N (1.1 equivalent) was added and the reaction allowed to warm to room temperature and stirred overnight under an atmosphere of nitrogen. The reaction mixture was concentrated and the residue partitioned between EtOAc and H₂O and the organic phase washed with sat. NaHCO₃, brine, dried (MgSO₄ or Na₂SO₄), filtered and concentrated. The crude product was purified by column chromatography or preparative TLC.

Method 15

Sulfonylation Procedure III

To a solution of L-Pro-L-4-(3-dimethylaminopropoxy)-Phe-OMe [prepared using the procedure described in Method 10] (1 equivalent) in CH₂Cl₂ was added Et₃N (5 equivalents) followed by the appropriate sulfonyl chloride (1.1 equivalent). The reaction was allowed to warm to room temperature and stirred overnight under an atmosphere of nitrogen. The mixture was concentrated, dissolved in EtOAc, washed with sat. NaHCO₃ and 0.2 N citric acid. The aqueous phase was made basic with solid NaHCO₃ and the product extracted with EtOAc. The organic phase was washed with brine, dried (MgSO₄ or Na₂SO₄), filtered and concentrated. The crude methyl ester was purified by preparative TLC. The corresponding acid was prepared using the procedure described in Method 7.

Method 16

Hydrogenation Procedure II

To a methanol (10 -15 mL) solution of the azlactone, was added NaOAc (1 equivalent) and 10% Pd/C. This mixture was placed on the hydrogenator at 40 psi H₂. After 8 - 16 hours, the reaction mixture was filtered through a pad of Celite and the filtrate concentrated to yield the dehydrodipeptide methyl ester. The ester was dissolved in dioxane/H₂O (5- 10 mL), to which was added 0.5 N NaOH (1.05 equivalents). After stirring for 1- 3 hours, the reaction mix was concentrated and the residue was redissolved in H₂O and washed with EtOAc. The aqueous phase was made acidic with 0.2 N HCl and the product was extracted with EtOAc. The combined organic phase was washed with brine (1 x 5 mL), dried (MgSO₄ or Na₂SO₄), filtered and concentrated to yield the acid as approximately a 1:1 mixture of diastereomers.

Method 17

Tert-Butyl Ester Hydrolysis Procedure II

The *tert*-butyl ester was dissolved in CH₂Cl₂ (5 mL) and treated with TFA (5 mL). The reaction was complete in 1-3 hours at which time the reaction mixture was concentrated and the residue dissolved in H₂O and concentrated. The residue was redissolved in H₂O and lyophilized to yield the desired product.

Example 1

25

Synthesis of *N*-(Toluene-4-sulfonyl)cycloleucyl-L-phenylalanine

Cycloleucine was *N*-sulfonated with toluenesulfonyl chloride using the procedure described in Method 1. The title compound was then prepared as a white solid by following Method 3 using the methyl ester of phenylalanine which was subsequently hydrolyzed in a 1:1 solution of MeOH:H₂O containing NaOH to provide for the title compound.

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NMR data was as follows:

¹H NMR (300 MHZ, DMSO-*d*₆): δ = 8.19 (s, 1H), 7.84 (d, 2H, *J* = 8.46 Hz), 7.64 (d, 1H, *J* = 8.25 Hz), 7.52 (d, 2H, *J* = 8.25 Hz), 7.42 (m, 2H), 7.36 (m, 2H), 4.50 (m, 1H), 3.62 (m, 1H), 3.15 (m, 2H), 2.54 (s, 3H), 1.98 (m, 4H), 1.60 (m, 2H), 1.35 (m, 2H).

¹³C NMR (300 MHZ, CD₃OD): δ = 176.35, 174.52, 145.17, 141.77, 138.37, 131.23, 130.02, 128.45, 122.08, 109.47, 71.29, 55.72, 39.03, 37.96, 24.68, 22.00.

Mass Spectroscopy: (FAB) 431 (M+H).

Example 2

Synthesis of *N*-(2-Methoxycarbonylphenylsulfonyl)- α - methylalanyl-L-phenylalanine

The title compound was prepared by first preparing the benzyl ester R⁶ = -OCH₂- ϕ) in the manner described in Method 3 which ester was then dissolved in ethanol and hydrogenated in the manner of Method 4. The crude product was crystallized from EtOAc/Hexane to afford the title compound as a glassy semi-solid.

NMR data was as follows:

¹H NMR (CD₃OD, 300 MHZ): δ = 7.90 (m, 1H); 7.54 (m, 3H); 5.50 (bs, 5H); 4.32 (m, 1H); 3.76 (s, 3H); 3.00 (m, 1H); 2.78 (m, 1H); 1.12 (s, 3H); 1.05 (s, 3H).

¹³C NMR (CD₃OD, 300 MHZ): δ = 176.33, 176.25, 170.20, 143.32, 139.15, 134.22, 133.21, 132.85, 131.97, 131.02, 130.60, 129.85, 128.12, 61.60, 56.46, 54.41, 39.09, 31.23, 27.28, 26.15.

Mass Spectroscopy: (-FAB) 447 (M-H), 469 (M-2H+Na).

Example 3

**Synthesis of
N-(Toluene-4-sulfonyl)-L-
(2-methyl)proline-L-phenylalanine**

5

L-(2-methyl)proline was prepared by the method of Seebach, *J. Am. Chem. Soc.*, 105:5390 (1983). The title compound was then prepared by treating L-(2-methyl)proline with TsCl and NaOH in H₂O, to give after acidification, extraction, drying with MgSO₄, and evaporation, N-(Toluene-4-sulfonyl)-L-(2-methyl)Pro-OH. This product was treated with H-Phe-OBnHCl, BOP, and NMM in DMF, to give after aqueous workup and flash chromatography, N-(toluene-4-sulfonyl)-L-(2-methyl)Pro-Phe-OBn. This product was treated with 10% Pd on C in THF, and the mixture was shaken under H₂. The mixture was filtered through celite and evaporated to give the title compound as a clear oil.

15

NMR data was as follows:

¹H NMR (DMSO-*d*₆, 300 MHz): δ = 7.68 (d, *J* = 8.2 Hz, 2H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.28-7.16 (m, 5H), 4.53-4.46 (m, 1H), 3.36-3.30 (m, 2H), 3.24-3.11 (m, 2H), 3.00 (dd, *J* = 13.8 Hz, *J* = 8.7 Hz, 1H), 2.37 (s, 3H), 1.91-1.88 (m, 1H), 1.66-1.54 (m, 3H).

20

¹³C NMR (DMSO-*d*₆, 75 MHz): δ = 173.0, 172.7, 143.0, 137.4, 137.3, 129.5, 129.2, 128.1, 127.3, 126.4, 68.8, 53.5, 49.3, 40.6, 36.6, 22.3, 22.2, 21.0.

Mass Spectroscopy: (+FAB, 3-nitrobenzyl alcohol) 453 (M+Na).

25

Example 4

**Synthesis of
N-(Benzyl-4-sulfonyl)-cycloleucyl-
L-(4-amino-isonicotinoyl)phenylalanine Ethyl Ester**

30

N-(Benzyl-4-sulfonyl)-cycloleucyl-L-(4-amino)phenylalanine ethyl ester was prepared in the manner described above in the general procedures using appropriately protected amino acid/amino acid ester starting materials. After deprotection, N-(Benzyl-4-sulfonyl)-cycloleucyl-L-(4-amino)phenylalanine

ethyl ester was dissolved in dichloromethane with an excess (~ 1.1 eq.) of triethylamine and isonicotinic acid chloride (~ 1.1 eq.) to provide for the title compound.

NMR data was as follows:

5 ¹H NMR (CDCl₃): δ = 8.77 (d, 2H), 8.15 (s, 1H), 7.70 (d, 2H), 7.52 (d, 2H), 7.37 (s, 5H), 7.20 (d, 2H), 7.12 (d, 1H), 4.75 (m, 1H), 4.29 (s, 2H), 4.14 (q, 2H), 3.20-2.97 (m, 2H), 2.52 (s, 3H), 2.46 (m, 1H), 2.33 (m, 1H), 1.76-1.64 (m, 6H), 1.24 (t, 3H).

10 ¹³C NMR (CDCl₃): δ = 172.9, 171.3, 163.6, 150.7, 142.0, 136.2, 133.0, 130.7, 130.0, 128.9, 128.8, 128.8, 120.9, 120.4, 74.1, 61.4, 60.9, 53.5, 37.2, 36.2, 36.1, 34.8, 23.0, 22.8, 13.9.

Example 5

15 Synthesis of *N*-(Benzylsulfonyl)-cycloleucyl-L-phenylalanine

The title compound was prepared following the procedure of Example 1.

NMR data was as follows:

20 ¹H NMR (CD₃OD): δ = 7.63 (d, 1H), 7.50-7.27 (m, 1H), 4.80 (s, 1H), 4.37 (s, 2H), 3.34-3.10 (m, 2H), 2.29-1.68 (m, 8H).

¹³C NMR (CD₃OD): δ = 176.5, 174.6, 138.2, 132.4, 131.1, 130.7, 1296.6, 128.0, 76.8, 62.0, 55.0, 48.0, 38.3, 38.2, 24.6, 24.6.

Example 6

25 Synthesis of *N*-(Benzylsulfonyl)cycloleucyl- L-(4-amino-(2-bromobenzoyl))phenylalanine Ethyl Ester

30 Cycloleucine was *N*-sulfonated with α-toluenesulfonyl chloride using the procedure described in Method 1. The title compound was then prepared following the procedure of Example 4.

NMR data was as follows:

¹H NMR (CDCl₃): δ = 7.68 - 7.53 (m, 4H), 7.48 - 7.19 (m, 8H), 7.11 (m, 1H), 4.78 (m, 1H), 4.30 (s, 2H), 4.19 (q, 2H), 3.25-2.95 (m, 2H), 2.53 (s, 3H), 2.46 (m, 1H), 2.33 (m, 1H), 1.84-1.50 (m, 6H), 1.25 (t, 3H).

¹³C NMR (CDCl₃): δ = 172.9, 171.3, 165.4, 137.8, 136.4, 133.5,
5 132.8, 131.7, 130.8, 130.1, 129.8, 128.9, 128.8, 128.7, 127.8, 120.1,
74.1, 61.4, 60.8, 53.5, 37.2, 36.2, 36.1, 34.8, 23.0, 22.9, 13.9.

Example 7

10 Synthesis of *N*-(Benzyl-4-sulfonyl)cycloleucyl- L-(4-aminoisonicotinoyl)phenylalanine

The title compound was prepared from the product of Example 4 using the procedure described in Method 7.

NMR data was as follows:

15 ¹H NMR (DMSO-*d*₆): δ = 10.61 (s, 1H), 8.74 (d, 2H), 7.85 (t, 2H),
7.59 (d, 2H), 7.32 (m, 5H), 7.11 (d, 2H), 4.49 (m, 2H), 3.96 (m, 1H), 3.06 (br s, 2H), 2.63 (s, 3H), 2.30 (m, 1H), 1.89 (m, 2H), 1.78-1.40 (m, 5H).

¹³C NMR (DMSO-*d*₆): δ = 172.8, 171.8, 163.9, 136.7, 135.4, 131.4,
20 130.1, 128.4, 121.9, 120.0, 116.6, 109.8, 97.9, 73.7, 57.6, 55.5, 46.7,
36.7, 34.7, 33.8, 28.8, 23.4.

Example 8

25 Synthesis of *N*-(Benzylsulfonyl)cycloleucyl- L-(4-*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-Butyl Ester

Cycloleucine was *N*-sulfonated with α-toluenesulfonyl chloride using the procedure described in Method 1 and then coupled to L-Tyr(H)-O-*t*-butyl using conventional amino acid coupling procedures to provide for *N*-(benzylsulfonyl)cycloleucyl-L-tyrosine *t*-butyl ester.

30 The title compound was then prepared by combining into a suitable reaction flask 1 eq. of *N*-(benzylsulfonyl)cycloleucyl-L-tyrosine *t*-butyl ester with ~ 1 eq. DMAP in methylene chloride to which was added ~ 1 eq. Et₃N

and ~1.2 eq. dimethylcarbamy chloride. The reaction flask was then capped tightly, and swirled to obtain a homogeneous solution. The reaction solution was then heated to 40°C. After 48 hours, TLC of the resulting colorless solution indicates complete conversion. EtOAc (50 mL) and hexanes (50 mL) were added to the reaction mixture, and the resulting solution was washed with 3 x 50 mL 0.5 M citric acid, 2 x 50 mL water, 2 x 50 mL 10% K₂CO₃, and 1 x 50 mL sat. NaCl. The solution was then dried with anhydrous MgSO₄, filtered and the solvent evaporated to obtain 8.00 g (99%) of the title compound as a clear oil, which solidifies upon standing. The solid was recrystallized from 5:3:2 heptane/EtOAc/CH₂Cl₂.

NMR data was as follows:

¹H NMR (CDCl₃): δ = 7.38 (m, 5H), 7.19 (d, 2H), 7.06 (m, 3H), 4.67 (m, 1H), 4.30 (s, 2H), 3.17-2.95 (m, 8H), 2.51 (s, 3H), 2.45 (m, 1H), 2.30 (m, 1H), 1.84-1.53 (m, 6H), 1.41 (s, 9H).

¹³C NMR (CDCl₃): δ = 172.7, 170.1, 154.9, 150.5, 133.3, 130.8, 130.2, 129.0, 128.8, 128.7, 121.7, 82.2, 74.2, 60.7, 54.0, 37.4, 36.5, 36.3, 36.2, 36.1, 34.8, 27.8, 23.2, 22.9.

Example 9

Synthesis of *N*-(Toluene-4-sulfonyl)-*N*-methylcycloleucyl- D-phenylalanine Methyl Ester

Cycloleucine was *N*-sulfonated with toluenesulfonyl chloride using the procedure described in Method 1. The title compound was then prepared by coupling D-Phe-O-methyl using conventional amino acid coupling procedures.

NMR data was as follows:

¹H NMR (CDCl₃): δ = 7.67 (d, 2H), 7.35-7.20 (m, 8H), 4.80 (m, 1H), 3.74 (s, 3H), 3.29-2.98 (m, 2H), 2.83 (s, 3H), 2.43 (s, 3H), 2.35 (m, 1H), 2.18 (m, 1H), 1.80-1.34 (m, 6H).

^{13}C NMR (CDCl_3): $\delta = 173.2, 172.0, 143.4, 139.4, 136.3, 129.8, 129.3, 128.7, 127.0, 126.7, 74.2, 53.5, 52.2, 37.7, 35.1, 35.0, 34.5, 22.9, 22.8, 21.4.$

5

Example 10

Synthesis of *N*-(Benzylsulfonyl)-*N*-methylcycloleucyl- L-(4-*N,N*-dimethylcarbamyloxy)phenylalanine

10 The title compound was prepared from the product of Example 8 using the procedure described in Method 11.

NMR data was as follows:

^1H NMR (CDCl_3): $\delta = 7.38$ (m, 5H), 7.19 (d, 2H), 7.03 (m, 3H), 6.69 (br s, 1H), 4.79 (m, 1H), 4.29 (m, 2H), 3.26-2.97 (m, 2H), 3.08 (s, 3H), 2.99 (s, 3H), 2.50 (s, 3H), 2.43 (m, 1H), 2.24 (m, 1H), 1.83-1.55 (m, 6H).

15

^{13}C NMR (CDCl_3): $\delta 174.2, 173.7, 155.2, 150.5, 133.1, 130.8, 130.2, 128.9, 128.9, 128.8, 121.9, 74.1, 60.5, 53.3, 36.6, 36.3, 36.2, 36.1, 34.6, 23.2, 23.0.$

Preparative Example A

20

Synthesis of *N*-(Toluene-4-sulfonyl)-*N*-methyl-cycloleucyl- D-(4-*N,N*-dimethylcarbamyloxy)phenylalanine *t*-butyl ester

25 The title compound was prepared following the procedure for the synthesis of Example 8 substituting D-Tyr(H)-O-*t*-butyl ester for L-Tyr(H)-O-*t*-butyl ester and employing *N*-(toluene-4-sulfonyl)-*N*-methyl-cycloleucine rather than *N*-(benzylsulfonyl)cycloleucine.

NMR data was as follows:

30 ^1H NMR (CDCl_3): $\delta 7.68$ (d, 2H), 7.31 - 7.15 (m, 5H), 7.04 (d, 2H), 4.68 (m, 1H), 3.21 - 2.97 (m, 2H), 3.08 (s, 3H), 2.99 (s, 3H), 2.83 (s, 3H), 2.43 - 2.29 (m, 4H), 2.21 (m, 1H), 1.84 - 1.33 (m, 15H).

Preparative Example B

Synthesis of
N-(Benzylsulfonyl)-*N*-methyl-(α -methyl)alaninyl-
L-(4-*N,N*-dimethylcarbamyloxy)phenylalanine *tert*-Butyl Ester

5 The title compound was prepared following the procedure for the synthesis of Example 8 substituting *N*-methyl-(α -methyl)alanine for *N*-methylcycloleucine of Example 8.

NMR data was as follows:

¹H NMR (CDCl₃): δ = 7.49 (m, 2H), 7.36 (m, 3H), 7.19 (d, 2H), 7.02
10 (d, 2H), 6.53 (d, 1H), 4.75 (m, 1H), 4.37 (m, 2H), 3.14-2.96 (m, 2H), 3.10 (s, 3H), 3.01 (s, 3H), 2.47 (s, 3H), 1.52 (s, 3H), 1.44 (s, 12H).

¹³C NMR (CDCl₃): δ = 173.6, 170.6, 154.9, 150.5, 133.2, 131.0,
130.4, 129.3, 128.7, 128.6, 121.7, 82.5, 64.6, 59.7, 53.5, 37.1, 36.6,
15 36.3, 32.6, 27.8, 25.7, 24.2.

Example 11

Synthesis of
N-(Benzylsulfonyl)-*N*-methyl-(α -methyl)alaninyl-
L-(4-*N,N*-dimethylcarbamyloxy)phenylalanine

20 The title compound was prepared from the product of Preparative Example B using the procedure described in Method 11.

NMR data was as follows:

¹H NMR (CDCl₃): δ = 7.48 (m, 2H), 7.36 (m, 3H), 7.17 (d, 2H), 7.02
(d, 2H), 6.40 (d, 1H), 4.82 (m, 1H), 4.35 (dd, 2H), 3.28-2.96 (m, 2H),
25 3.08 (s, 3H), 3.00 (s, 3H), 2.45 (s, 3H), 1.48 (s, 3H), 1.32 (s, 3H).

¹³C NMR (CDCl₃): δ = 177.3, 174.5, 173.3, 155.2, 150.5, 133.1,
131.0, 130.3, 128.8, 121.9, 64.5, 59.5, 53.1, 36.6, 36.3, 32.3, 25.4, 24.0.

Example 12

**Synthesis of
N-(Toluene-4-sulfonyl)-N-methylcycloleucyl-
D-(4-N,N-dimethylcarbamyloxy)phenylalanine**

5 The title compound was prepared from the product of Preparative
Example A using the procedure described in Method 11.

NMR data was as follows:

^{13}C NMR (CDCl_3): δ = 174.3, 173.9, 155.1, 150.5, 143.5, 138.9,
133.2, 130.2, 129.8, 126.9, 122.0, 74.2, 53.5, 44.5, 36.6, 36.3, 35.2,
10 35.0, 34.4, 23.1, 22.9, 21.3.

Example 13

**Synthesis of
N-(Toluene-4-sulfonyl)-L-(2-methyl)proline-L-
15 (4-N-methyl, N-(2-dimethylaminoethyl)carbamyloxy)
phenylalanine t-butyl ester**

A 400 mg solution of N-(toluene-4-sulfonyl)-L-(2-methyl)proline-L-
phenylalanine (400mg) (example 3), (2S)-2-amino-3-{4-[(2-dimethylamino-
20 ethyl)-methyl-carbamoyloxy]-phenyl-propionic acid tert-butyl ester (650
mg), HOBt (210 mg), 4-methyl morpholine (0.78 mL) in DMF (10 mL) was
stirred at 0° C. 1-[3-(Dimethylaminopropyl)-3-ethylcarbodiimide
hydrochloride (311 mg) was added to the solution. The ice bath was
removed after 10 minutes. The reaction was stirred at room temperature for
25 4 hours. Ethyl acetate (20 mL) was added to the solution. Thereafter the
solution was washed with saturated NaHCO_3 solution (30 mL, 2X), then with
brine and dried over MgSO_4 . The solvent was evaporated by vacuum, and
the residue flash chromatographed using silica gel in methanol/chloroform
(5:95) to give 300 mg of the desired product.

30 MS:[PCI (isobutane)] $[\text{M} + \text{H}]^+$ 631

Example 14

**Synthesis of
N-(Toluene-4-sulfonyl)-L-(2-methyl)proline-L-
(4-N-methyl, N-(2-dimethylaminoethyl)carbamyloxy) phenylalanine**

5

The starting N-(Toluene-4-sulfonyl)-L-(2-methyl)proline-L-(4-N-methyl, N-(2-dimethylaminoethyl)carbamyloxy)phenylalanine t-butyl ester (270 mg) was dissolved in HCl/dioxane (4M, 10mL). The reaction was stirred at room temperature for 6 hours. The solvent was evaporated in vacuo. The residue was recrystallized from acetonitrile/ethyl acetate to give 147 mg of the desired product.

10

MS: [(-)ESI] [M-H]⁻ 573

Example 15

15

**Synthesis of
N-(4-Fluoro-phenylsulfonyl)-L-(2-methyl)proline-L-
(4-N,N-dimethylcarbamyloxy)phenylalanine tert-butyl ester**

A solution of N-(4-fluoro-benzenesulfonyl)-2-methyl-L-prolyl-L-tyrosine-t-butyl ester (690 mg) in pyridine (15 mL) was treated at once with dimethylcarbamyl chloride (441 mg) under exclusion of moisture. The reaction mixture was stirred at 50° C overnight, evaporated and the residue flash chromatographed on 100 g silica gel. Elution with 1 % methanol / chloroform gave 550 mg of the desired product.

20

25

MS: [(+)ESI], [M+NH₄]⁺ 595

Example 16

30

**Synthesis of
N-(4-Fluoro-phenylsulfonyl)-L-(2-methyl)proline-L-
(4-N,N-dimethylcarbamyloxy)phenylalanine**

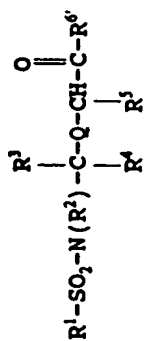
The title compound was prepared from the product of Example 15 using the procedure described in Method 11.

MS:[(-)ESI], [M-H] 520

0915095-072098

Other compounds prepared by the methods described above include those set forth in Table II below:

09125095-073098
060570 96092160



R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = -C(O)NR' ² - R'	Example No.
<i>p</i> -CH ₃ -φ-	-CH ₃	-CH ₃	-CH ₃	<i>p</i> -(nitro)benzyl-	-OCH ₂ CH ₃	H	13
<i>p</i> -CH ₃ -φ-	-CH ₃	-CH ₃	-CH ₃	-CH ₂ -φ	-OH	H	14
<i>p</i> -CH ₃ -φ-	-CH ₃	-CH ₃	-CH ₃	<i>p</i> -[(1-Boc-piperidin-4-yl)C(O)NH-]benzyl-	-OCH ₃	H	15
<i>p</i> -CH ₃ -φ-	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		-CH ₂ -φ	-OH	H	16
φCH ₂ -	-CH ₃	-CH ₃	-CH ₃	-CH ₂ -φ	-OCH ₂ CH ₃	H	17
<i>p</i> -CH ₃ -φ-	-CH ₃	-CH ₃	-CH ₃	<i>p</i> -[(piperidin-4-yl)C(O)NH-]benzyl-	-OCH ₃	H	18
φCH ₂ -	-CH ₃	-CH ₃	-CH ₃	-CH ₂ -φ	-OH	H	19

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = -C(O)NR ⁷ - R ⁷	Example No.
<i>p</i> -CH ₃ -φ-	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - CH ₂ CH ₂ - (cyclohexyl)		-CH ₂ -φ	-OH	H	20
<i>p</i> -CH ₃ -φ-	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(pyridin-4-yl)C(O)NH-]benzyl-	-OCH ₂ CH ₃	H	21
<i>p</i> -CH ₃ -φ-	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(2-bromophenyl)C(O)NH-]benzyl-	-OH	H	22
<i>p</i> -CH ₃ -φ-	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(1-Boc-piperidin-4-yl)C(O)NH-]benzyl-	-OCH ₃	H	23
<i>p</i> -CH ₃ -φ-	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(pyridin-4-yl)C(O)NH-]benzyl-	-OCH ₃	H	24
<i>p</i> -CH ₃ -φ-	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(2-Boc-1,2,3,4-tetrahydroisoquinolin-1-yl)C(O)NH-]benzyl-	-OCH ₃	H	25
<i>p</i> -CH ₃ -φ-	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(pyridin-4-yl)C(O)NH-]benzyl-	-OH	H	26

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = $\begin{matrix} \text{C}(\text{O})\text{NR}^7 \\ \text{R}^7 \end{matrix}$	Example No.
<i>p</i> -CH ₃ -φ-	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(2-bromophenyl)C(O)NH-]benzyl-	-OCH ₃	H	27
<i>p</i> -CH ₃ -φ-	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(4-(CH ₃) ₂ NC(O)O-)benzyl-	-OCH ₃	H	28
<i>p</i> -CH ₃ -φ-	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(4-(CH ₃) ₂ NC(O)O-)benzyl-	-OCH ₂ CH ₃	H	29
<i>p</i> -CH ₃ -φ-	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(4-(CH ₃) ₂ NC(O)O-)benzyl-	-OH	H	30
<i>p</i> -CH ₃ -φ-	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(1-methylpiperidin-4-yl)-O-]benzyl-	-OCH ₂ CH ₃	H	31
<i>p</i> -CH ₃ -φ-	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclobutyl)		-CH ₂ -φ	-OCH ₃	H	32
<i>p</i> -CH ₃ -φ-	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		-CH ₃	<i>p</i> -(pyridin-4-yl)-C(O)NHbenzyl-	-OCH ₃	H	33

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = -C(O)NR ⁷ -	Example No.
<i>p</i> -CH ₃ -φ	CH ₃ -	R ³ /R ⁴ = cyclic 3 carbon atoms (cyclobutyl)		-CH ₂ -φ	-OH	H	34
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		-CH ₃	<i>p</i> -(pyridin-4-yl-C(O)NH)benzyl-	-OH	H	35
<i>p</i> -CH ₃ -φ	CH ₃ -	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(1-methylpiperidin-4-yl)-O]-benzyl-	-OCH ₃	H	36
<i>p</i> -CH ₃ -φ	CH ₃ -	R ³ /R ⁴ = -CH ₂ CH ₂ - (cyclopropyl)		-CH ₂ -φ	-OH	H	37
<i>p</i> -CH ₃ -φ	CH ₃ -	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(piperidin-4-yl)C(O)NH]-benzyl-	-OH	H	38
<i>p</i> -CH ₃ -φ	CH ₃ -	R ³ /R ⁴ = -CH ₂ CH ₂ - (cyclopropyl)		-CH ₂ -φ	-OCH ₃	H	39
<i>p</i> -CH ₃ -φ	CH ₃ -	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(1-methylpiperidin-4-yl)-O]-benzyl-	-OH	H	40
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyl)		-CH ₃	<i>p</i> -[(1-methylpiperidin-4-yl)-O]-benzyl-	-OCH ₂ CH ₃	H	41

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = $\begin{matrix} \text{C}(\text{O})\text{NR}^7 \\ \text{R}^7 \end{matrix}$	Example No.
$\phi\text{-CH}_2\text{-}$	CH ₃ -	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(1-methylpiperidin-4-yl)-O-]benzyl-	-OCH ₃	H	42
$\phi\text{-CH}_2\text{-}$	CH ₃ -	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(1-methylpiperidin-4-yl)-O-]benzyl-	-OCH ₂ CH ₃	H	43
<i>p</i> -CH ₃ - ϕ -	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidiny)		-CH ₃	<i>p</i> -[(1-methylpiperidin-4-yl)-O-]benzyl-	-OH	H	44
$\phi\text{-CH}_2\text{-}$	CH ₃ -	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(2-bromophenyl)C(O)NH-]benzyl-	-OCH ₂ CH ₃	H	45
$\phi\text{-CH}_2\text{-}$	CH ₃ -	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(1-methylpiperidin-4-yl)-O-]benzyl-	-OH	H	46
<i>p</i> -CH ₃ - ϕ -	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidiny)		-CH ₃	<i>p</i> -[(4-methylpiperazin-1-yl)C(O)O-]benzyl-	-OC(CH ₃) ₃	H	47
<i>p</i> -CH ₃ - ϕ -	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidiny)		-CH ₃	<i>p</i> -[(CH ₃) ₂ NC(O)O-]benzyl-	-OC(CH ₃) ₃	H	48

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	Q = $\frac{-C(O)NR'}{R'}$	Example No.:
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		-CH ₃	<i>p</i> -[(4-methylpiperazin-1-yl)C(O)O-]benzyl-	-OH	H	49
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		-CH ₃	<i>p</i> -[(CH ₃) ₂ NC(O)O-]benzyl-	-OH	H	50
<i>p</i> -CH ₃ -φ	R ² /R ³ = -(CH ₂) ₃ -		-CH ₃	<i>p</i> -[(morpholin-4-yl)C(O)O-]benzyl-	-OC(CH ₃) ₃	H	51
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		-CH ₃	<i>p</i> -[(morpholin-4-yl)C(O)O-]benzyl-	-OH	H	52
<i>p</i> -CH ₃ -φ	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(CH ₃) ₂ NC(O)O-]benzyl-	-OC(CH ₃) ₃	H	53
<i>p</i> -CH ₃ -φ	R ² /R ³ = cyclic 3 carbon atoms (L-pyrrolidinyI)		-CH ₃	<i>p</i> -[(morpholin-4-yl)C(O)O-]benzyl-	-O-CH ₂ -O-C(O)- C(CH ₃) ₃	H	54
<i>p</i> -CH ₃ -φ	-CH ₃	R ³ /R ⁴ = -CH ₂ CH ₂ CH ₂ CH ₂ - (cyclopentyl)		<i>p</i> -[(2-bromophenyl)C(O)NH-]benzyl-	-OCH ₂ CH ₃	H	55

Example 56

***In vitro* Assay For Determining Binding of
Candidate Compounds to VLA-4**

5 An *in vitro* assay was used to assess binding of candidate compounds to $\alpha_4\beta_1$ integrin. Compounds which bind in this assay can be used to assess VCAM-1 levels in biological samples by conventional assays (e.g., competitive assays). This assay is sensitive to IC_{50} values as low as about 1nM.

10 The activity of $\alpha_4\beta_1$ integrin was measured by the interaction of soluble VCAM-1 with Jurkat cells (e.g., American Type Culture Collection Nos. TIB 152, TIB 153, and CRL 8163), a human T-cell line which expresses high levels of $\alpha_4\beta_1$ integrin. VCAM-1 interacts with the cell surface in an
15 $\alpha_4\beta_1$ integrin-dependent fashion (Yednock, et al. J. Biol. Chem., 1995, 270:28740).

20 Recombinant soluble VCAM-1 was expressed as a chimeric fusion protein containing the seven extracellular domains of VCAM-1 on the N-terminus and the human IgG₁ heavy chain constant region on the C-terminus. The VCAM-1 fusion protein was made and purified by the manner described by Yednock, *supra*.

25 Jurkat cells were grown in RPMI 1640 supplemented with 10% fetal bovine serum, penicillin, streptomycin and glutamine as described by Yednock, *supra*.

30 Jurkat cells were incubated with 1.5 mM $MnCl_2$ and 5 $\mu g/mL$ 15/7 antibody for 30 minutes on ice. Mn^{+2} activates the receptor to enhance ligand binding, and 15/7 is a monoclonal antibody that recognizes an activated/ligand occupied conformation of $\alpha_4\beta_1$ integrin and locks the

molecule into this conformation thereby stabilizing the VCAM-1/ $\alpha_4\beta_1$ integrin interaction. Yednock, et al., *supra*. Antibodies similar to the 15/7 antibody have been prepared by other investigators (Luque, et al, 1996, J. Biol. Chem. 271:11067) and may be used in this assay.

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Cells were then incubated for 30 minutes at room temperature with candidate compounds, in various concentrations ranging from 66 μ M to 0.01 μ M using a standard 5-point serial dilution. 15 μ L soluble recombinant VCAM-1 fusion protein was then added to Jurkat cells and incubated for 30 minutes on ice. (Yednock et al., *supra*).

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Cells were then washed two times and resuspended in PE-conjugated goat F(ab')₂ anti-mouse IgG Fc (Immunotech, Westbrook, ME) at 1:200 and incubated on ice, in the dark, for 30 minutes. Cells were washed twice and analyzed with a standard fluorescence activated cell sorter ("FACS") analysis as described in Yednock, et al., *supra*.

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Compounds having an IC₅₀ of less than about 15 μ M possess binding affinity to $\alpha_4\beta_1$.

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When tested in this assay, each of the compounds in Examples 1-55 has an IC₅₀ of 15 μ M or less.

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Example 57

***In vitro* Saturation Assay For Determining Binding of Candidate Compounds to $\alpha_4\beta_1$**

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The following describes an *in vitro* assay to determine the plasma levels needed for a compound to be active in the Experimental Autoimmune

Encephalomyelitis ("EAE") model, described in the next example, or in other *in vivo* models.

5 Log-growth Jurkat cells are washed and resuspended in normal animal plasma containing 20 $\mu\text{g/ml}$ of the 15/7 antibody (described in the above example).

10 The Jurkat cells are diluted two-fold into either normal plasma samples containing known candidate compound amounts in various concentrations ranging from 66 μM to 0.01 μM , using a standard 12 point serial dilution for a standard curve, or into plasma samples obtained from the peripheral blood of candidate compound-treated animals.

15 Cells are then incubated for 30 minutes at room temperature, washed twice with phosphate-buffered saline ("PBS") containing 2% fetal bovine serum and 1mM each of calcium chloride and magnesium chloride (assay medium) to remove unbound 15/7 antibody.

20 The cells are then exposed to phycoerythrin-conjugated goat F(ab')_2 anti-mouse IgG Fc (Immunotech, Westbrook, ME), which has been adsorbed for any non-specific cross-reactivity by co-incubation with 5% serum from the animal species being studied, at 1:200 and incubated in the dark at 4°C for 30 minutes.

25 Cells are washed twice with assay medium and resuspended in the same. They are then analyzed with a standard fluorescence activated cell sorter ("FACS") analysis as described in Yednock et al. J. Biol. Chem., 1995, 270:28740.

The data is then graphed as fluorescence versus dose, e.g., in a normal dose-response fashion. The dose levels that result in the upper plateau of the curve represent the levels needed to obtain efficacy in an *in vivo* model.

5 This assay may also be used to determine the plasma levels needed to saturate the binding sites of other integrins, such as the $\alpha_9\beta_1$ integrin, which is the integrin most closely related $\alpha_4\beta_1$ (Palmer et al, 1993, J. Cell Bio., 123:1289). Such binding is predictive of *in vivo* utility for inflammatory conditions mediated by $\alpha_9\beta_1$ integrin, including by way of example, airway
10 hyper-responsiveness and occlusion that occurs with chronic asthma, smooth muscle cell proliferation in atherosclerosis, vascular occlusion following angioplasty, fibrosis and glomerular scarring as a result of renal disease, aortic stenosis, hypertrophy of synovial membranes in rheumatoid arthritis, and inflammation and scarring that occur with the progression of ulcerative
15 colitis and Crohn's disease.

Accordingly, the above-described assay may be performed with a human colon carcinoma cell line, SW 480 (ATTC #CCL228) transfected with cDNA encoding α_9 integrin (Yokosaki et al., 1994, J. Biol. Chem.,
20 269:26691), in place of the Jurkat cells, to measure the binding of the $\alpha_9\beta_1$ integrin. As a control, SW 480 cells which express other α and β_1 subunits may be used.

Accordingly, another aspect of this invention is directed to a method for
25 treating a disease in a mammalian patient, which disease is mediated by $\alpha_9\beta_1$, and which method comprises administering to said patient a therapeutically effective amount of a compound of this invention. Such compounds are preferably administered in a pharmaceutical composition described herein above. Effective daily dosing will depend upon the age, weight, condition of
30 the patient which factors can be readily ascertained by the attending

clinician. However, in a preferred embodiment, the compounds are administered from about 20 to 500 $\mu\text{g/kg}$ per day.

Example 58

In vivo Evaluation

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The standard multiple sclerosis model, Experimental Autoimmune (or Allergic) Encephalomyelitis ("EAE"), was used to determine the effect of candidate compounds to reduce motor impairment in rats or guinea pigs.

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Reduction in motor impairment is based on blocking adhesion between leukocytes and the endothelium and correlates with anti-inflammatory activity in the candidate compound. This model has been previously described by Keszthelyi et al., Neurology, 1996, 47:1053-1059, and measures the delay of onset of disease.

15

Brains and spinal cords of adult Hartley guinea pigs were homogenized in an equal volume of phosphate-buffered saline. An equal volume of Freund's complete adjuvant (100 mg *mycobacterium tuberculosis* plus 10 ml Freund's incomplete adjuvant) was added to the homogenate. The mixture was emulsified by circulating it repeatedly through a 20 ml syringe with a peristaltic pump for about 20 minutes.

20

Female Lewis rats (2-3 months old, 170-220 g) or Hartley guinea pigs (20 day old, 180-200 g) were anesthetized with isoflurane and three injections of the emulsion, 0.1 ml each, were made in each flank. Motor impairment onset is seen in approximately 9 days.

25

Candidate compound treatment began on Day 8, just before onset of symptoms. Compounds were administered subcutaneously ("SC"), orally ("PO") or intraperitoneally ("IP"). Doses were given in a range of 10mg/kg to 200 mg/kg, bid, for five days, with typical dosing of 10 to 100 mg/kg SC, 10 to 50 mg/kg PO, and 10 to 100 mg/kg IP.

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Antibody GG5/3 against $\alpha_4\beta_1$ integrin (Keszthelyi et al., Neurology, 1996, 47:1053-1059), which delays the onset of symptoms, was used as a positive control and was injected subcutaneously at 3 mg/kg on Day 8 and 11.

5

Body weight and motor impairment were measured daily. Motor impairment was rated with the following clinical score:

	0	no change
10	1	tail weakness or paralysis
	2	hindlimb weakness
	3	hindlimb paralysis
	4	moribund or dead

15

A candidate compound was considered active if it delayed the onset of symptoms, e.g., produced clinical scores no greater than 2 or slowed body weight loss as compared to the control.

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When tested in this *in vivo* assay, the compound of Example 47 was active.

Example 59

Asthma Model

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Inflammatory conditions mediated by $\alpha_4\beta_1$ integrin include, for example, airway hyper-responsiveness and occlusion that occurs with chronic asthma. The following describes an asthma model which can be used to study the *in vivo* effects of the compounds of this invention for use in treating asthma.

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Following the procedures described by Abraham et al, J. Clin. Invest, 93:776-787 (1994) and Abraham et al, Am J. Respir Crit Care Med, 156:696-703 (1997), both of which are incorporated by reference in their entirety, compounds of this invention are formulated into an aerosol and

administered to sheep which are hypersensitive to *Ascaris suum* antigen. Compounds which decrease the early antigen-induced bronchial response and/or block the late-phase airway response, e.g., have a protective effect against antigen-induced late responses and airway hyper-responsiveness ("AHR"), are considered to be active in this model.

Allergic sheep which are shown to develop both early and late bronchial responses to inhaled *Ascaris suum* antigen are used to study the airway effects of the candidate compounds. Following topical anesthesia of the nasal passages with 2% lidocaine, a balloon catheter is advanced through one nostril into the lower esophagus. The animals are then intubated with a cuffed endotracheal tube through the other nostril with a flexible fiberoptic bronchoscope as a guide.

Pleural pressure is estimated according to Abraham (1994). Aerosols (see formulation below) are generated using a disposable medical nebulizer that provides an aerosol with a mass median aerodynamic diameter of 3.2 μm as determined with an Andersen cascade impactor. The nebulizer is connected to a dosimeter system consisting of a solenoid valve and a source of compressed air (20 psi). The output of the nebulizer is directed into a plastic T-piece, one end of which is connected to the inspiratory port of a piston respirator. The solenoid valve is activated for 1 second at the beginning of the inspiratory cycle of the respirator. Aerosols are delivered at V_T of 500 ml and a rate of 20 breaths/minute. A 0.5% sodium bicarbonate solution only is used as a control.

To assess bronchial responsiveness, cumulative concentration-response curves to carbachol can be generated according to Abraham (1994). Bronchial biopsies can be taken prior to and following the initiation of treatment and 24 hours after antigen challenge. Bronchial biopsies can be preformed according to Abraham (1994).

An *in vitro* adhesion study of alveolar macrophages can also be performed according to Abraham (1994), and a percentage of adherent cells is calculated.

5 Aerosol Formulation

A solution of the candidate compound in 0.5% sodium bicarbonate/saline (w/v) at a concentration of 30.0 mg/mL is prepared using the following procedure:

10 A. Preparation of 0.5% Sodium Bicarbonate / Saline Stock Solution:
100.0 mL

	Ingredient	Gram / 100.0 mL	Final Concentration
	Sodium Bicarbonate	0.5 g	0.5 %
15	Saline	q.s. ad 100.0 mL	q.s. ad 100%

Procedure:

1. Add 0.5g sodium bicarbonate into a 100 mL volumetric flask.
2. Add approximately 90.0 mL saline and sonicate until dissolved.
- 20 3. Q.S. to 100.0 mL with saline and mix thoroughly.

B. Preparation of 30.0 mg/mL Candidate Compound: 10.0 mL

	Ingredient	Gram / 10.0 mL	Final Concentration
25	Candidate Compound	0.300 g	30.0 mg/mL
	0.5% Sodium Bicarbonate / Saline Stock Solution	q.s. ad 10.0 mL	q.s ad 100%

Procedure:

1. Add 0.300 g of the candidate compound into a 10.0 mL
5 volumetric flask.
2. Add approximately 9.7 mL of 0.5% sodium bicarbonate / saline
stock solution.
3. Sonicate until the candidate compound is completely dissolved.
4. Q.S. to 10.0 mL with 0.5% sodium bicarbonate / saline stock
10 solution and mix thoroughly.

Using a conventional oral formulation, compounds of this invention
would be active in this model.

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